(30)

No. 04-607
Title: Laboratory Corporation of America Holdings, dba LabCorp, Petitioner
v.
Metabolite Laboratories, Inc., et al.
Docketed: November 5, 2004
Lower Ct: United States Court of Appeals for the Federal Circuit
Case Nos.: (03-1120)
Decision Date: June 8, 2004
Rehearing Denied: August 5, 2004
Questions Presented

~~Date~~~	~~~~~~~Proceedings and Orders~~~~~~~~~~~~~~~~~~~~~~~~
Nov 3 2004	Petition for a writ of certiorari filed. (Response due December 6, 2004)
Dec 3 2004	Brief of respondents Metabolite Laboratories, Inc., et al. in opposition filed.
Dec 14 2004	Reply of petitioner Laboratory Corporation of America Holdings, dba as LabCorp filed. (Distributed)
Dec 15 2004	DISTRIBUTED for Conference of January 7, 2005.
Jan 10 2005	DISTRIBUTED for Conference of January 14, 2005.
Jan 18 2005	DISTRIBUTED for Conference of January 21, 2005.
Feb 11 2005	Supplemental brief of petitioner Laboratory Corporation of America Holdings, dba as LabCorp filed.
Feb 14 2005	DISTRIBUTED for Conference of February 18, 2005.
Feb 22 2005	DISTRIBUTED for Conference of February 25, 2005.
Feb 28 2005	The Solicitor General is invited to file a brief in this case expressing the views of the United States limited to the following question: Respondent's patent claims a method for detecting a form of vitamin B deficiency, which focuses upon a correlation in the human body between elevated levels of certain amino acids and deficient levels of vitamin B. The method consists of the following: First, measure the level of the relevant amino acids using any device, whether the device is, or is not, patented; second, notice whether the amino acid level is elevated and, if so, conclude that a vitamin B deficiency exists. Is the patent invalid because one cannot patent "laws of nature, natural phenomena, and abstract ideas"? Diamond v. Diehr, 450 U.S. 175, 185 (1981).
Aug 26 2005	Brief amicus curiae of United States filed.
Sep 2 2005	Supplemental brief of petitioner Laboratory Corporation of America Holdings, dba as LabCorp filed. (Distributed)
Sep 7 2005	DISTRIBUTED for Conference of September 26, 2005.
Oct 3 2005	DISTRIBUTED for Conference of October 7, 2005.
Oct 11 2005	DISTRIBUTED for Conference of October 14, 2005.
Oct 24 2005	DISTRIBUTED for Conference of October 28, 2005.
Oct 31 2005	Petition GRANTED limited to Question 3 presented by the petition for a writ of certiorari.
Nov 2 2005	Having been advised by the Chief Justice that he now realizes that he should have recused himself from participation in this case, and does now recuse himself, the Court vacates its order of Monday, October 31, 2005. The Court has reconsidered the petition for certiorari, which is granted but limited to question three as presented in the petition. The Chief Justice has not participated in the vote to withdraw the order of October 31, 2005 or

in the instant reconsideration of the petition for certiorari.

Nov 17 2005 Extension of time within which to file the joint appendix and petitioner's brief on the merits to and including December 23, 2005.

Nov 17 2005 Extension of time within which to file respondent's brief on the merits to and including February 6, 2006.

Dec 15 2005 Brief amicus curiae of Intellectual Property Owners Association in Support of Neither Party filed.

Dec 22 2005 Brief amicus curiae of People's Medical Society filed.

Dec 23 2005 Brief amicus curiae of United States filed.

Dec 23 2005 Brief of petitioner Laboratory Corporation of America Holdings, dba LabCorp filed.

Dec 23 2005 Joint appendix filed. (Jt.appendix in 2 vols.)

Dec 23 2005 Supplemental appendix filed.

Dec 23 2005 Brief amicus curiae of American Clinical Laboratory Association filed.

Dec 23 2005 Brief amicus curiae of American Heart Association filed.

Dec 23 2005 Brief amicus curiae of Financial Services Industry filed.

Dec 23 2005 Brief amicus curiae of Patients Not Patents, Inc. filed.

Dec 23 2005 Brief amicus curiae of International Business Machines Corporation in support of neither party filed.

Dec 23 2005 Brief amicus curiae of Association of the Bar of the City of New York in support of neither party filed.

Dec 23 2005 Brief amicus curiae of American Express Company in support of neither party filed.

Dec 23 2005 Brief amicus curiae of Computer & Communications Industry Association filed.

Dec 23 2005 Brief amici curiae of Affymetrix, Inc. and Professor John H. Barton filed.

Dec 23 2005 Brief amici curiae of American Medical Association, et al. filed.

Dec 23 2005 Brief amicus curiae of AARP filed.

Dec 23 2005 Brief amicus curiae of Public Patent Foundation filed.

Jan 23 2006 SET FOR ARGUMENT on Tuesday, March 21, 2006.

Jan 24 2006 Motion of the Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument filed.

Feb 6 2006 Brief of respondents Metabolite Laboratories, Inc. and Competitive Technologies, Inc. filed. (Distributed)

Feb 6 2006 Brief amicus curiae of Franklin Pierce Law Center filed. (Distributed)

Feb 6 2006 Brief amicus curiae of American Intellectual Property Law Association filed. (Distributed)

Feb 6 2006 Brief amicus curiae of Boston Patent Law Association filed. (Distributed)

Feb 6 2006 Brief amici curiae of Perlegen Sciences, Inc. and Mohr, Davidow Ventures filed. (Distributed)

Feb 6 2006 Brief amicus curiae of Federal Circuit Bar Association filed. (Distributed)

Feb 7 2006 CIRCULATED.

Feb 14 2006 Record received from U.S.C.A. for Federal Circuit. (1 box)

Feb 21 2006 Motion of the Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument GRANTED. The Chief Justice took no part in the consideration or decision of this motion.

Feb 27 2006 Record received from U.S.D.C. for the Eastern District of Colorado. (5 boxes)

Mar 9 2006	Reply of petitioner Laboratory Corporation of America Holdings, dba LabCorp filed. (Distributed).
Mar 21 2006	Argued. For petitioner: Jonathan S. Franklin, Washington, D.C. For United States as amicus curiae: Thomas G. Hunger, Deputy Solicitor General, Department of Justice, Washington, D.C. For respondents: Miguel A. Estrada, Washington, D.C.

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No. 04-

IN THE

Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS (doing business as LabCorp),

Petitioner,

v.

METABOLITE LABORATORIES, INC. and COMPETITIVE TECHNOLOGIES, INC.,

Respondents.

Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR A WRIT OF CERTIORARI

JOHN P. HIGGINS
ALSTON & BIRD, LLP
Bank of America Plaza
101 South Tryon Street
Suite 4000
Charlotte, NC 28280
(704) 444-1000

JONATHAN S. FRANKLIN*
CATHERINE E. STETSON
JESSICA L. ELLSWORTH
HOGAN & HARTSON L.L.P.
555 Thirteenth Street, N.W.
Washington, D.C. 20004
(202) 637-5766

* Counsel of Record

Counsel for Petitioner

WILSON-EPES PRINTING CO., INC. – (202) 789-0096 – WASHINGTON, D. C. 20001

Supreme Court, U.S.
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QUESTIONS PRESENTED

1. Whether liability can be imposed for willfully inducing patent infringement under 35 U.S.C. § 271(b) based solely on evidence that a party has disseminated a basic scientific fact to others.

2. Whether an express limitation in a patent claim can be ignored so as to allow the patent to cover the exact opposite of what was claimed.

3. Whether a method patent setting forth an indefinite, undescribed, and non-enabling step directing a party simply to "correlat[e]" test results can validly claim a monopoly over a basic scientific relationship used in medical treatment such that any doctor necessarily infringes the patent merely by thinking about the relationship after looking at a test result.

PARTIES TO THE PROCEEDINGS AND RULE 29.6 STATEMENT

Petitioner in this case is Laboratory Corporation of America Holdings (doing business as LabCorp) ("LabCorp").

LabCorp has no parent corporations. Wellington Management Company, L.L.P., a publicly held mutual fund, owns ten percent or more of LabCorp's stock. No other publicly held company owns ten percent or more of LabCorp's stock.

Respondents are Metabolite Laboratories, Inc. and Competitive Technologies, Inc.

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IN THE

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LABORATORY CORPORATION OF AMERICA HOLDINGS (doing business as LabCorp),

Petitioner,

v.

METABOLITE LABORATORIES, INC. and COMPETITIVE TECHNOLOGIES, INC.,

Respondents.

Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR A WRIT OF CERTIORARI

Petitioner Laboratory Corporation of America Holdings ("LabCorp") respectfully petitions this Court for a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit in this case.

OPINIONS BELOW

The opinion of the Federal Circuit is reported at 370 F.3d 1354 and is reproduced at page 1a of the appendix to this petition ("App."). The order of the District Court denying LabCorp's motion for judgment as a matter of law or a new trial is unreported and is reproduced at App. 34a.

JURISDICTION

The judgment of the Federal Circuit was entered on June 8, 2004. On August 5, 2004, the Federal Circuit denied a

timely filed petition for rehearing or rehearing en banc. This Court has jurisdiction pursuant to 28 U.S.C. § 1254(1).

STATUTORY PROVISIONS INVOLVED

Pertinent statutes are set forth in the appendix to this brief.

INTRODUCTION

The holding of the Federal Circuit in this case is truly extraordinary. The court construed a patent to confer on respondents a legally-protected monopoly to bar any doctor in the Nation from even *thinking* about a well-known scientific correlation. It then went even further, holding—in conflict with other Federal Circuit decisions—that petitioner LabCorp indirectly "induced" such infringement merely by publishing truthful information informing doctors of this basic scientific fact. And further compounding its errors, the Federal Circuit violated well-established tenets of patent law by expanding the patent beyond its express terms, and by upholding its validity.

This case implicates a well-recognized and intractable conflict in the lower court. And the case is of substantial national importance, given the severe threat to patient care posed by the Federal Circuit's holding that a party can violate the patent laws merely by informing doctors of a basic medical fact critical to treatment decisions. The conflict has necessarily engendered nationwide confusion, and the Federal Circuit has not been able to reconcile the conflict on its own. If this Court does not intervene, the result will be continuing and intolerable uncertainty for patent holders, practitioners, and those in LabCorp's position who seek to disseminate basic medical facts needed to ensure the health of the Nation's populace. The Court should therefore grant certiorari to resolve the conflicts on these important issues.

STATEMENT OF THE CASE

A. The '658 Patent.

This case involves Patent No. 4,940,658 (the "Patent"), which seeks a legally-protected monopoly over the thought

processes of doctors. Specifically, the patent claims a right to prevent doctors from *thinking* about a scientific correlation used for patient care. The correlation relates to homocysteine, an amino acid found naturally in blood serum. The Patent's "inventors" assert that they were the first to discover a connection between elevated levels of total homocysteine in body fluids and possible deficiencies in two basic vitamins, vitamin B12 (cobalamin) and folic acid (folate).

It is disputed whether the inventors were in fact the first to notice this correlation. But there is no dispute that, well before they applied for their patent, it was well-known that elevated levels of homocysteine correlated with other conditions. Most important, it had been known since at least 1969 —more than 15 years before the filing of the Patent application—that elevated homocysteine was connected to increased risk of heart disease. *See, e.g.*, A4828-29.[1] Elevated homocysteine has also been connected with other conditions, including renal disease, dehydration, vitamin B6 deficiency, inborn enzyme deficiencies, hypothyroidism, lupus, pregnancy-related conditions, and decreased cognitive function. *See, e.g.*, A8377, A8430. And respondent Competitive Technologies, Inc. ("CTI") has itself noted that elevated levels are also associated with Alzheimer's disease, chronic fatigue syndrome, and rheumatoid arthritis. *See* A7977.

The Patent primarily claims a new method for assaying homocysteine levels in bodily fluids, which requires the use of gas chromatography and mass spectrometry ("GCMS"). *See* A929, col. 41, lns. 2-57. That method, which is described in Claims 1-12 of the Patent, is not at issue in this appeal. LabCorp has paid and *continues* to pay royalties whenever it uses the patented assay method. A4744-46.[2]

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[1] "A___" refers to the Appendix filed in the Court of Appeals.

[2] The Patent is now owned by CTI. CTI licensed the Patent to respondent Metabolite Laboratories, Inc. ("Metabolite"), which in turn sublicensed to LabCorp's predecessor certain Metabolite

This case arises because the Patent also claimed a much broader monopoly. The disputed claim in this case, Claim 13, seeks to patent the basic scientific connection between elevated homocysteine levels and the possibility of certain vitamin deficiencies. In its entirety, Claim 13 seeks to patent

> [a] method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> assaying a body fluid for an elevated level of total homocysteine; and
>
> correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

App. 3a.

Claim 13 is thus a "method" patent consisting of only two steps. *First*, one must assay a body fluid for an elevated level of total homocysteine. It does not matter what assay method is used, for Claim 13 applies no matter how one tests for homocysteine. *Second*, one must "correlat[e]" the elevated level of homocysteine with a deficiency of cobalamin or folate. The term "correlating" is not further defined, and nothing in the patent says precisely what it means to "correlate" an elevated level of homocysteine with vitamin deficiencies. The entire second step was added to overcome a prior art rejection based on Section 102 of the Patent Act. *See* A973, 975.

Respondents, however, have shown how broadly they interpret Claim 13. It is their theory that, unless a license is granted and a royalty paid, every one of the thousands of doctors who orders one of the millions of homocysteine tests performed for patients nationwide necessarily infringes the Patent because the doctor looks at the test result and

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technology relating to performing "licensed assays" that "us[ed] methods and materials falling within the claims of [the '658 patent]." A7952.

allegedly *thinks* that the result *might* indicate something about the existence or non-existence of a vitamin deficiency. Under respondents' theory—now endorsed by the Federal Circuit—when a doctor orders a test and then thinks in his or her mind about the possible connection between the test result and a vitamin deficiency, that doctor has infringed the Patent by performing the patented "correlating" step.

B. LabCorp's Performance of Homocysteine Tests.

Respondents have also taken their claim further yet. LabCorp is the Nation's second largest laboratory testing company. Rather than sue every doctor for infringement for *thinking* about a possible indication of a vitamin deficiency when reviewing a test result, respondents sued LabCorp—which indisputably committed no direct infringement—on the theory that LabCorp contributes to or induces infringement by performing homocysteine tests for doctors and by allegedly informing doctors of the basic medical fact that elevated homocysteine is connected to vitamin deficiencies.

LabCorp has performed two different types of homocysteine tests. One is a "panel test" that assays for homocysteine along with three other metabolites. LabCorp pays royalties to respondents when it performs this test because this test employs the patented GCMS method. *See* A4744-45. LabCorp also performs a "single homocysteine test" that assays just for homocysteine. Initially, LabCorp also used the CGMS method for this test, and thus paid royalties to respondents.

Unlike the panel test, the single homocysteine test is of limited utility to doctors screening for vitamin deficiencies. That is because, as the Patent itself notes, homocysteine may be elevated in cases of cobalamin *or* folate deficiency, *or* as the result of other conditions, and a test *only* for homocysteine therefore cannot itself diagnose specific vitamin deficiencies. A911, col. 5, lns. 45-48, 64-66, A4293, 4825. The patent specification itself notes that it could be "extremely dangerous" to diagnose and treat a cobalamin or folate defi-

ciency based on just an elevated homocysteine result. *See* A909, col. 1, lns. 46-55. Indeed, one of the '658 inventors wrote to LabCorp in 1992 advising that it was not good medical practice to use a single metabolite—such as homocysteine—to diagnose cobalamin or folate deficiencies. A7950.

Single homocysteine tests *are* useful, however, in screening patients for risk of heart disease. It was discovered as early as 1969 that there is a link between elevated levels of homocysteine and increased risk of heart disease. *See* A8374, A7980, A8010, A8029. This medical knowledge became more widespread by the 1990s and resulted in an increase in demand for tests solely of homocysteine. *See* A5141, A5144.

In May 1998, LabCorp entered into a research agreement with Abbott Laboratories to test Abbott's new immunoassay method for assaying for homocysteine. Abbott's method was faster and less labor-intensive than the GCMS method identified in the Patent—a crucial advance in light of the increased demand for single homocysteine tests.

As a result, in 1998 LabCorp stopped using the licensed method for single homocysteine blood tests and began using Abbott's method. *See* A8519.[3] LabCorp continued, however, to use respondent CTI's licensed method to perform the panel test and homocysteine assays on urine samples, and it continued to pay royalties on those assays. A4744-45. On November 2, 1998, LabCorp notified respondent Metabolite (CTI's licensee) that it had begun using the Abbott method for single homocysteine assays, and that it would no longer pay royalties for such tests. A8473.

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[3] The sublicense agreement specifically provides that LabCorp could terminate the agreement with respect to licensed assays of homocysteine if "a more cost effective commercial alternative is available that does not infringe a valid and enforceable claim of the Licensed Patents." A7957.

C. District Court Proceedings.

In 1999, CTI and Metabolite sued LabCorp for direct and indirect infringement of the Patent and for breach of the sublicense agreement. A102.[4] Plaintiffs alleged that LabCorp's performance of single homocysteine tests using the Abbott immunoassay method infringed Claim 13. *See* A2404.

The District Court issued a pre-trial order interpreting Claim 13. A219. The court defined "elevated" as "raised above the normal range." A220. The court defined "correlating" as meaning "to establish a mutual or reciprocal relationship between," further observing that " '[c]orrelating' is a verb, and must * * * comprise a discrete, sequential process step." A221. The court subsequently granted summary judgment to LabCorp on direct infringement because LabCorp itself did not do any "correlating" of test results. A1. But the court denied LabCorp's motion for summary judgment on induced infringement. A2.

The case was tried to a jury beginning in November 2001. The court denied LabCorp's motion for JMOL at the close of the evidence, candidly informing counsel that the jury was "probably going to flip a coin." A5406. The jury returned a verdict against LabCorp for contributory and induced infringement. And while the trial evidence demonstrated that fewer than 20% of test results showed *elevated* homocysteine levels (as expressly required to satisfy the limitations of Claim 13), App. 32a-33a, the jury nonetheless awarded damages to plaintiffs based on *every* single homocysteine test LabCorp performed. That amounted to $1,019,365.01 to CTI on its patent claim, and $3,652,724.61 to Metabolite on its breach of contract claim. A5-6. The jury also found LabCorp's infringement to be willful, and returned a verdict in favor of plaintiffs on LabCorp's invalidity defenses. A6-7.

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[4] CTI, the patent holder, sued LabCorp for patent infringement, Metabolite, the licensee, sued LabCorp for breach of contract.

In November 2002, the District Court denied LabCorp's post-trial motion for JMOL or a new trial, and doubled the jury's patent damages award. App. 36a. The court also enjoined LabCorp from performing "*any* homocysteine-only test, including without limitation homocysteine-only tests via the Abbott method." App. 38a (emphasis added and internal quotation omitted).

D. Court of Appeals Decision.

1. Claim Construction. A panel of the Federal Circuit affirmed by a 2-1 vote. As an initial matter, LabCorp had contended that for the "correlating" step to have any real meaning, it must require a physician to confirm that a patient with elevated homocysteine is in fact suffering from a vitamin deficiency as evidenced by actual physical symptoms. LabCorp explained that the patent itself notes that many people with elevated homocysteine do *not* suffer from vitamin deficiencies, and that the "inventors" themselves had determined such deficiencies in their patients by looking for physical symptoms. A910-911. Thus, because respondents presented no evidence that doctors who look at the results of single homocysteine tests ever confirm the existence of vitamin deficiencies, LabCorp argued that the doctors did not infringe the patent and that LabCorp could not be held liable for induced or contributory infringement.

The panel rejected this argument, holding that Claim 13

> does not require a further association between the level of total homocysteine and [physical symptoms]. *The claim only requires association of homocysteine levels with vitamin deficiencies. It requires no further correlation to confirm the relationship to vitamin deficiencies.*

App. 8a (emphasis added). *See also* App. 12a ("the claim language does not require a confirmatory step linking these conditions to diagnosed or apparent symptoms").

In other words, the court held that a doctor infringes the patent merely by looking at a test result and *thinking* in his or her mind that there is an "association of homocysteine levels with vitamin deficiencies." App. 8a. Once the doctor has thought about this basic scientific association after looking at a homocysteine test result, he or she has performed the patented "correlation." According to the court, no further steps—such as confirming that the patient actually *has* a vitamin deficiency—are required to infringe the patent.

Then, the Federal Circuit expanded the patent even further. Whereas Claim 13 clearly states that it covers only the assaying and correlation of "an *elevated* level of total homocysteine," A929 (emphasis added), the panel majority held that the patent is infringed even by test results that are *not* elevated—more than 80% of all test results. The majority held that it is immaterial whether a test result is elevated because the accepted definition of "correlating" is to establish a "mutual or reciprocal" relationship. In so holding, however, the court ignored the clear language of the patent requiring correlation only of *elevated* levels. App. 12a.

Judge Schall dissented on this point. In his view, by holding that the Patent is infringed by the correlation of test results showing *unelevated* homocysteine levels, "the majority impermissibly expand[ed] the scope of claim 13 beyond the actual words of the claim." App. 29a. As he explained, "[t]here is no language in Claim 13 addressing unelevated levels of homocysteine, nor language that unelevated levels of homocysteine are to be correlated with the absence of a vitamin deficiency." App. 31a. Thus, "[i]f the patient's homocysteine levels are not 'elevated,' by the plain language of the claim, there is no 'correlating' to be done." *Id.* In other words, whatever the word "correlate" stands for on its own, a doctor can infringe Claim 13 only by correlating an *elevated* homocysteine level with a cobalamin or folate deficiency.

2. Induced Infringement. LabCorp also argued (1) that it could not be liable for contributory infringement because there are substantial *non*-infringing uses for single

homocysteine tests—most importantly, to assess for risk of heart disease; and (2) that it could not be liable for induced infringement because respondents presented no evidence that LabCorp specifically intended to induce infringement.

The Federal Circuit did not reach the contributory infringement argument. Instead, it held that LabCorp could be held liable for induced infringement merely because certain educational and informational materials published by LabCorp state the basic medical fact "that elevated total homocysteine correlates to cobalamin/folate deficiency." App. 15a According to the panel, the dissemination of this scientific fact to doctors constituted induced infringement because LabCorp thereby "promoted total homocysteine assays for detecting cobalamin/folate deficiency." *Id.*[5]

3. Invalidity. The panel also rejected LabCorp's related argument that if Claim 13 were to be construed as broadly as respondents contended, it would be invalid. *First*, LabCorp had argued that Claim 13 was "indefinite," and therefore invalid, because nothing in the patent actually informs practitioners how to "correlate," which the District Court had held must entail a "discrete, sequential process step." A221. The panel, however, found that Claim 13 was not indefinite because "the claim construction exercise at the trial court produced a discernible and clear meaning." App. 16a. The

[5] In fact, the panel was incorrect as a factual matter. LabCorp's Directory of Services—described by the panel as "stat[ing] that elevated total homocysteine correlates to cobalamin/folate deficiency"—in fact *expressly* refers physicians to the *panel test* (on which LabCorp continues to pay royalties) to determine folate deficiencies. A8501 (referring to "megaloblastic anemia profile" panel test), A8505 (same), A8499 (panel test). The only other "evidence" of intent the panel identified—two Continuing Medical Education articles—nowhere promote using a total homocysteine test to detect vitamin deficiencies. One discusses the royalty-bearing panel test. *See* A9622. The other simply discusses the significance of homocysteine as a risk factor for *heart disease*. A9610.

panel did not further elaborate on this holding, which presumably referred to its view, expressed earlier in the opinion, that the "correlating" step merely requires a doctor to look at a test result and think about the possible connection to vitamin deficiencies.

Second, LabCorp argued that Claim 13 lacked an adequate "written description." The panel rejected that argument, holding that the record showed "that physicians in homocysteine research * * * understood from the specification that the '658 patent inventors possessed the 'correlating' step at the time they filed the patent application," and that "LabCorp's own expert and employees understood the meaning of 'correlating.' " App. 17a.

Third, LabCorp argued that Claim 13 did not sufficiently "enable" doctors to practice the patented "correlating" step. The panel, however, held that "the correlating step is well within the knowledge of one of skill in this art" because "[t]he correlating step is a simple conclusion that a cobalamin/folate deficiency exists *vel non* based on the assaying step." App. 18a. In support of this holding, the panel cited statements in the Patent that elevated homocysteine levels "are indicative of cobalamin and/or folate deficiency" in that "the higher the level, the stronger the indication." App. 18a (quoting '658 Patent, col. 9, ll. 26-29).[6]

4. Willfulness, Enhanced Damages, Injunction, and Attorneys' Fees. The panel also affirmed the District Court's award of enhanced damages based on the jury's finding of willful infringement. App. 26a. And it affirmed

[6] LabCorp also argued that Claim 13 was invalid based on "prior art" because it had long been known that elevated levels of homocysteine were connected to conditions such as those described in the Patent. The court rejected these arguments, holding that the prior art did not set forth the *precise* correlation between *total* homocysteine (as opposed to one of its principal components) and cobalamin or folate deficiencies. App. 19a.

the injunction prohibiting LabCorp from directly performing homocysteine tests under any testing method. App. 27a.

Eight months after it entered final judgment on the merits, the District Court also entered an award of more than $1.1 million in attorneys' fees and costs against LabCorp, based on the earlier finding of willful infringement. LabCorp separately appealed that judgment to the Federal Circuit, and that appeal was stayed pending the outcome of the merits appeal.[7]

On August 5, 2004, the Federal Circuit denied LabCorp's timely petition for rehearing or rehearing en banc. App. 40a.

REASONS FOR GRANTING THE WRIT

I. THE COURT SHOULD RESOLVE THE CONFLICT OVER THE REQUIREMENTS FOR INDUCED INFRINGEMENT.

A. The Conflict Is Well-Recognized And Intractable.

A principal controversy underlying this case stems from two inconsistent Federal Circuit opinions issued over a decade ago regarding the requirements for induced infringement under Section 271(b) of the Patent Act: *Manville Sales Corp.* v. *Paramount Sys., Inc.*, 917 F.2d 544 (Fed. Cir. 1990), and *Hewlett-Packard Co.* v. *Bausch & Lomb Inc.*, 909 F.2d 1464 (Fed. Cir. 1990). Section 271(b) permits a patentee to bring an action against "[w]hoever actively induces" patent infringement. 35 U.S.C. § 271(b). Although this Court has never directly addressed the issue, it is clear that there are at least two prerequisites for inducement to infringement: (1) a showing that the conduct being induced is in fact direct infringement and (2) proof of intent to induce infringement. *See, e.g., Minnesota Min. &*

[7] Concurrently with this petition, LabCorp has filed a motion with the Federal Circuit requesting entry of judgment on that appeal based on the affirmance of the merits appeal, while expressly preserving all of LabCorp's arguments against that affirmance for review by this Court.

Mfg. Co. v. *Chemque, Inc.*, 303 F.3d 1294, 1305 (Fed. Cir. 2002).

The Federal Circuit, however, is hopelessly divided as to what suffices to meet the intent requirement. Indeed, the Federal Circuit itself has recently recognized the longstanding schism. As the court lamented just weeks ago, "there is a lack of clarity concerning whether the required intent must be merely to induce the specific acts or additionally to cause an infringement." *Insituform Technologies, Inc.* v. *CAT Contracting, Inc.*, — F.3d —, 2004 WL 2240591, at *18 (Fed. Cir. Oct. 4, 2004).[8] The decision below directly implicates this conflict, and holds that the intent requirement can be satisfied merely by the publication of truthful information regarding a basic scientific fact. This Court should grant certiorari to resolve the conflicting standards announced by the Federal Circuit—a conflict that has been percolating for over a decade, that is at the core of the extraordinary holding below, and that the Federal Circuit has shown no ability to resolve on its own.

The conflict is both clear and direct. In *Hewlett-Packard*, 909 F.2d at 1469, the Federal Circuit held that the intent prong of inducement to infringe requires "proof of actual intent to cause the acts which constitute the infringement." According to this standard, a defendant may have the requisite intent by encouraging others to undertake infringing acts, even if the defendant believes that those acts do not constitute patent infringement and the defendant does not literally intend for patent infringement to occur. *See also Moba, B.V.* v. *Diamond Automation, Inc.*, 325 F.3d 1306, 1318 (Fed. Cir.), *cert. denied*, 124 S. Ct. 464 (2003). The court below applied the *Hewlett-Packard* standard. *See* App. 14a.

[8] Although the court noted the conflict in *Insituform*, it did not resolve the conflict because it found sufficient evidence under either standard. *Id.*

By contrast, in *Manville Sales*, 917 F.2d at 553, the Federal Circuit held that the intent prong for inducement to infringe requires the plaintiff to show that the alleged inducer "knowingly induced infringement." In other words,

> [i]t must be established that the defendant possessed specific intent to encourage another's infringement and not merely that the defendant had knowledge of the acts alleged to constitute inducement. The plaintiff has the burden of showing that the alleged infringer's actions induced infringing acts *and* that he knew or should have known his actions would induce actual infringements.

Id. (emphasis in original).

Thus, under the *Manville Sales* analysis, a party like LabCorp could only be liable for inducement to infringe if it knew or should have known its acts were inducing actual infringement. Simple " 'knowledge of the acts alleged to constitute infringement' is not enough." *Warner-Lambert Co.* v. *Apotex Corp.*, 316 F.3d 1348, 1363 (Fed. Cir. 2003) (citation omitted); *see also Ferguson Beauregard/Logic Controls* v. *Mega Sys., LLC*, 350 F.3d 1327, 1342 (Fed. Cir. 2003) (applying *Manville Sales* standard); *Minnesota Mining & Mfg. Co.*, 303 F.3d at 1305 (applying *Manville Sales* standard, but noting *Hewlett-Packard* alternative standard); *Mentor H/S, Inc.* v. *Medical Device Alliance, Inc.*, 244 F.3d 1365, 1379 (Fed. Cir. 2001) (applying *Manville Sales* standard).

The conflict also extends beyond patent law. The Federal Circuit has routinely declared that Section 271(b) imposes liability for "aiding and abetting" the commission of a legal wrong. *See, e.g., National Presto Indus., Inc.* v. *West Bend Co.*, 76 F.3d 1185, 1194-96 (Fed. Cir. 1996). Yet in its nonpatent cases, the court has held that liability for aiding and abetting a tort requires proof of a defendant's specific intent to violate the law. *See, e.g., United States* v. *Hitachi America, Ltd.*, 172 F.3d 1319, 1337 (Fed. Cir. 1999) ("legal authority in various civil and criminal contexts supports the view that liability for aiding or abetting requires, *inter alia*,

proof of knowledge of unlawfulness, also articulated as intent to violate the law"). The general aiding and abetting standard applied by the Federal Circuit in non-patent cases is consistent with its approach in *Manville Sales*. By contrast, the *Hewlett-Packard* standard applied in this case—which imposed liability on LabCorp based on the mere dissemination of truthful scientific information—is inconsistent with this general standard.

It is not only the Federal Circuit that has noticed this conflict; commentators have as well. Thus, one commentator has noted that "a clear definition of the mens rea required for inducement liability has eluded even the Federal Circuit." *Recent Cases, "Patent Law—Active Inducement of Infringement,"* 115 Harv. L. Rev. 1246, 1246 (Feb. 2002). And another has stated that the Federal Circuit "has faltered in its attempts to define the level of culpable intent required for a party to be guilty of inducement to infringe. By issuing conflicting decisions on the matter, the Federal Circuit has created a great deal of uncertainty in district courts as to the controlling standard." Michael N. Rader, *Toward A Coherent Law Of Inducement To Infringe: Why The Federal Circuit Should Adopt The* Hewlett-Packard *Standard For Intent Under § 271(b)*, 10 Fed. Circuit B.J. 299, 300 (2000). *See also* Robert O. Bolan & William C. Rooklidge, *Imputing Knowledge To Determine Willful Patent Infringement*, 24 Am. Intell. Prop. L. Ass'n Q.J. 157, 163 n.13 (1996) (intent standard for inducement liability is "totally unclear").

Even though the Federal Circuit's exclusive Patent Act jurisdiction generally precludes Circuit splits in patent cases, this Court has granted certiorari in the past when the Federal Circuit has shown that it cannot resolve an important question of patent law. *See, e.g., Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 727 (2002); *Warner-Jenkinson Co.* v. *Hilton Davis Chem. Co.*, 520 U.S. 17, 24 (1997). The Court should do so here. The conflict within the Federal Circuit has persisted for more than a

decade and the extended division in that court shows that the question has gone as far as it can in that Circuit. The time is thus ripe for this Court to intervene to bring certainty and consistency to the law. And, as next shown, this is the proper case in which to do so.

B. This Case Presents An Appropriate Vehicle For Resolving The Conflict.

This case is an especially appropriate vehicle for clarifying the standard required for induced infringement, given the minimal evidence that the Federal Circuit held constituted the requisite intent to infringe, and the harmful effect of the court's holding on patient care. The Federal Circuit held that LabCorp was guilty of inducement based *solely* on LabCorp's dissemination to doctors of a basic medical fact—that an elevated level of total homocysteine correlates with certain vitamin deficiencies. This evidence clearly would not satisfy the *correct* test for inducement—which should require a showing that a defendant specifically intended to infringe a patent, rather than just evidence that infringement may have been the result of the defendant's actions.

The evidence relied on by the Federal Circuit demonstrates no specific intent by LabCorp to induce any doctor to infringe the '658 patent. According to the Federal Circuit, the sole evidence of LabCorp's intent to induce infringement consisted of Continuing Medical Education articles and a Directory of Services—both general informational resources for doctors—which "state that elevated total homocysteine correlates to cobalamin/folate deficiency and that this deficiency can be treated with vitamin supplements." App. 15a. According to the court, "[t]he publications advocate use of the [homocysteine] assay to identify a need for cobalamin/folate supplements." *Id.* Based *only* on this evidence, and nothing else, the Federal Circuit held that "a reasonable jury could find intent to induce infringement because

LabCorp's articles state that elevated total homocysteine correlates to cobalamin/folate deficiency." *Id.*[9]

This case thus starkly presents the conflict. Applying the flawed *Hewlett-Packard* test, the Federal Circuit held that LabCorp willfully violated the patent laws merely by publishing general informational articles "stat[ing] that elevated total homocysteine correlates to cobalamin/folate deficiency"—in other words, by simply disseminating a basic scientific fact that is helpful to doctors seeking to diagnose and treat their patients. By contrast, decisions applying the *Manville Sales* standard have required much more before intent to induce can be found. Under that standard, recitation of a basic scientific fact cannot be induced infringement unless accompanied by overt guidance, instruction, or encouragement—in other words, proof of *specific intent*—that a patent be infringed.[10] Here, LabCorp has never provided directions or instructions to doctors or anyone else on how to infringe the '658 patent. To the contrary, LabCorp consistently honored its license agreement and paid royalties for

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[9] In fact, as noted above, the Federal Circuit misconstrued the evidence on which it relied. The cited statements referred to the *panel* test, on which LabCorp has always paid royalties, not the single homocysteine test at issue in this case. *See supra* n.5.

[10] *See, e.g., Biotec Biologische Naturverpackungen GmbH & Co. KG* v. *Biocorp, Inc.*, 249 F.3d 1341, 1351 (Fed. Cir. 2001) (defendant induced infringement by specifically instructing customers to process product so as to meet every limitation of patented claim); *Ferguson Beauregard*, 350 F.3d at 1342 (no induced infringement where no evidence that defendant knew or should have known his actions would induce infringement); *Micro Chem., Inc.* v. *Great Plains Chem. Co.*, 194 F.3d 1250, 1261 (Fed. Cir. 1999) (no induced infringement when undisputed facts did not establish the knowledge necessary to find specific intent to induce); 5 Donald S. Chisum, *Chisum on Patents* § 17-04[4][f] at 17-103 (2004) (citing decisions finding inducement where defendants gave "instructions and directions as to the infringing use").

the panel test, which uses the specific assay method covered by the Patent. A7952, A230-31. And LabCorp always understood and believed that the doctors who ordered *single* homocysteine tests were doing so to screen for risk of heart disease, not to diagnose vitamin deficiencies.

The facts of this case thus illustrate the grave dangers for medical testing and treatment of allowing such a relaxed test for inducement. Under the Federal Circuit's holding, any person—such as an author of a medical textbook—would be guilty of induced infringement if he or she simply published the basic scientific fact that elevated levels of homocysteine correlate to deficiencies of cobalamin or folate. For that is the sum total of the evidence which the Federal Circuit held constituted LabCorp's intent to induce—the publication to doctors of this basic medical fact. A truthful statement of medical fact—standing alone—cannot under any circumstances constitute a specific intent to infringe a patent.

To hold otherwise would dramatically transform the patent laws from an engine of discovery into a means of preventing the dissemination of basic scientific information. This Court has long recognized that scientific facts and laws of nature are outside the scope of patentable inventions. *See, e.g.*, *Diamond* v. *Diehr*, 450 U.S. 175, 185 (1981) ("[e]xcluded from * * * patent protection are laws of nature, natural phenomena, and abstract ideas"); *Gottschalk* v. *Benson*, 409 U.S. 63, 67 (1972) ("Phenomena of nature, though just discovered, * * * are not patentable, as they are the basic tools of scientific and technological work."); *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948) ("[P]atents cannot issue for the discovery of the phenomena of nature."); *Mackay Radio & Tel. Co.* v. *Radio Corp. of Am.*, 306 U.S. 86, 94 (1939). The reason for the rule is that scientific principles and laws of nature—which have existed throughout time—"ought not to be the subject of exclusive rights of any one person." *In re Meyer*, 688 F.2d 789, 795 (C.C.P.A. 1982) (*citing Le Roy* v. *Tatham*, 55 U.S. (14 How.) 156 (1852)).

In this case, the Federal Circuit improperly broadened this limited scope of the patent laws in at least two ways. First, the court incorrectly construed the Patent as conferring a monopoly over the thought processes of doctors, by holding that direct infringement occurs whenever a doctor looks at a homocysteine test result and thinks about a possible connection to vitamin deficiencies—regardless of what testing method is used and without requiring any further confirmation of an actual deficiency. *See supra* at 8-9.[11] But the court took its flawed holding a step further, by holding that a third party such as LabCorp, which indisputably committed no direct infringement, can be held liable for indirect infringement merely by reciting a medical fact. Given that no person can claim a patent over a scientific fact, it must follow that no person can be guilty of induced infringement merely by stating such a fact.

In sum, the Federal Circuit is itself hopelessly divided on these issues and this case presents the proper vehicle to resolve the conflict and restore certainty to the law. The Court should therefore grant certiorari to confirm that a party cannot be liable for patent infringement merely because it has informed doctors of a medical fact.[12]

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[11] The patent specification nowhere discloses that the correlating step can be performed in the physician's mind by merely looking at a homocysteine level test result. The patent teaches, rather, that physicians must perform other tests revealing a symptom of cobalamin or folate deficiency before it can be established that elevated homocysteine has any relationship with, or is caused by, a cobalamin or folate deficiency. A911, col. 5, ll. 40-63. This error, which is related to the Federal Circuit's errors on induced infringement and invalidity, is also presented for this Court's review. *See* S. Ct. R. 14.1(a) (Court will consider all issues "fairly included" in the questions presented).

[12] The errors outlined in this petition directly implicate the jury's findings of willful infringement and breach of contract, and the District Court's awards of enhanced damages and injunctive

II. THE DECISION BELOW CONFLICTS WITH THIS COURT'S DECISIONS ON CLAIM CONSTRUCTION AND INVALIDITY.

Certiorari is also warranted because the Federal Circuit's decision below conflicts with precedents of this Court, as well as the Federal Circuit's own precedents, on both patent claim construction and invalidity. *See* S. Ct. Rule 10(c). Given the importance of the case, and the clear errors committed by the Federal Circuit, the Court should grant certiorari to resolve these conflicts as well.

A. The Federal Circuit Impermissibly Ignored A Critical Claim Limitation That Was Added To Overcome The Prior Art.

This Court has made clear that the scope of a patent monopoly is strictly limited to the terms of the claim as drafted by the patent holder. As the Court has held, all limitations of a claim must be considered meaningful, and the focus of claim construction must begin with, and remain centered on, the language of the claims themselves.[13] The Federal Circuit

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relief, which all depend at least in part on the findings of infringement and validity. Accordingly, reversal of the Federal Circuit on infringement and validity requires reversal on these issues as well.

[13] *See, e.g., Sears, Roebuck & Co.* v. *Stiffel Co.*, 376 U.S. 225, 230 (1964) ("Once the patent issues, it is strictly construed" and "it cannot be used to secure any monopoly beyond that contained in the patent"); *Aro Mfg. Co.* v. *Convertible Top Replacement Co.*, 365 U.S. 336, 339-340 (1961) ("the claims made in the patent are the sole measure of the grant"); *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 374 (1996) ("Victory in an infringement suit requires a finding that the patent claim covers the alleged infringer's product or process, which in turn necessitates a determination of what the words in the claim mean.") (internal citations omitted); *Milcor Steel Co.* v. *George A. Fuller Co.*, 316 U.S. 143, 146 (1942) ("Out of all the possible permutations of elements which can be made from the specifications, [the patentee] reserves

previously has recognized this basic rule. *See, e.g., Texas Instruments, Inc.* v. *ITC*, 988 F.2d 1165, 1171 (Fed. Cir. 1993) (courts " 'can neither broaden nor narrow claims to give the patentee something different than what he has set forth.' ") (quotation omitted). Yet in this case the panel majority impermissibly ignored a claim limitation that was added to overcome the prior art (A973, A975) so as to allow a patent to cover the exact opposite of what was claimed. This departure from settled precedent also warrants this Court's review.

The dissent detailed the majority's error, noting that "the majority impermissibly expand[ed] the scope of claim 13 beyond the actual words of the claim." App. 29a. As the dissent carefully details, the majority rewrote the claim for purposes of its infringement analysis so that it covered not just what the claim actually specifies—correlation of "elevated" test results—but also the exact *opposite* of what it specifies—correlation of *un*elevated results, which comprise more than *80%* of all test results. Even after the court accepted the district court's construction that "elevated" means "raised above the normal range," *id.*, and even with claim language requiring one to "correlate[e] an *elevated* level," App. 8a, the majority held that tests revealing *no* elevated level were still infringing. In so holding, "the majority disregard[ed] the explicit limitation * * * that only an 'elevated' level of homocysteine can be 'correlated' with a vitamin deficiency." App. 31a. *See also id.* at 32a (majority "ignores the term 'elevated' ").

As Judge Schall further explained:

> There is no language in Claim 13 addressing unelevated levels of homocysteine, nor language that unelevated levels of homocysteine are to be correlated with the absence of a vitamin deficiency. Ordinary meaning thus

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for himself only those contained in the claims.") (quotation omitted).

> dictates that a patient's homocysteine level be "elevated" in order for a physician to practice claim 13. If the patient's homocysteine levels are not "elevated," by the plain language of the claim, there is no "correlating" to be done.

App. 31a.

That is precisely right. To infringe Claim 13, there must be a vitamin *deficiency*; for there to be a *deficiency*, there must be an "*elevated*" homocysteine level. Indeed, the preamble to the claim describes it as "[a] method for detecting a *deficiency of cobalamin or folate*." App. 3a. This "method" simply has no application where there is an *un*elevated homocysteine level, since such a normal test result can in no way detect a vitamin deficiency. Whatever the term "correlating" may mean by itself, the patent claim expressly covers only the correlation of *elevated* test results.

The majority's holding contravenes this Court's precedents in a striking and dangerous way. For the Federal Circuit has now held that a claim term can include the exact *opposite* of what the claim actually provides. If this holding is not corrected, practitioners will no longer be able to rely on the express claims of a patent. As this Court has held,

> [t]he limits of a patent must be known for the protection of the patentee, the encouragement of the inventive genius of others, and the assurance that the subject of the patent will be dedicated ultimately to the public. The statute seeks to guard against unreasonable advantages to the patentee and disadvantages to others arising from uncertainty as to their rights.

General Elec. Co. v. *Wabash Appliance Corp.*, 304 U.S. 364, 369 (1938). It is in large part for this reason that courts may

not redraft claims after-the-fact to sweep non-infringing conduct into the realm of infringing conduct.[14]

If not corrected, the Federal Circuit's holding will foster precisely the uncertainty that the patent laws are intended to prevent. The Court should grant certiorari to restore this certainty by confirming that a claim term cannot encompass the opposite of what was actually claimed.

B. A Patent That Simply Claims A Scientific "Correlation"—Without More—Is Indefinite, Insufficiently Described, And Non-Enabling.

The Court should also grant certiorari because the Federal Circuit contravened precedent by holding valid a patent that claims nothing but a scientific correlation. Claim 13 purports to claim a method consisting only of (1) assaying for elevated homocysteine levels, and (2) "correlating" elevated levels with vitamin deficiencies. App. 3a. Neither the claim nor the specification says anything about how one is to conduct the assay—indeed, Claim 13 covers *any* conceivable assay method. And more important, the patent says *nothing at all* about how one is to "correlate" an elevated level with a vitamin deficiency; that task is completely undescribed by the patent. Such a vague claim cannot be valid; for if it could be, parties could claim patent monopolies over basic scientific facts rather than any novel inventions.

To be valid, a patent must point out with particularity, and distinctly claim, the "invention." *See* 35 U.S.C. § 112 ¶ 2 (patent specification must "conclude with one or more claims particularly pointing out and distinctly claiming the subject

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[14] *See, e.g., Quantum Corp.* v. *Rodime, Plc*, 65 F.3d 1577, 1584 (Fed. Cir. 1995) ("Although we construe claims, if possible, so as to sustain their validity,* * * it is well settled that no matter how great the temptations of fairness or policy making, courts do not redraft claims.") (internal citation omitted); *Becton Dickinson & Co.* v. *CR Bard Inc.*, 922 F.2d 792, 799 n.6 (Fed. Cir. 1990) ("Nothing in any precedent permits judicial redrafting of claims.").

matter which the applicant regards as his invention"). An indefinite patent is invalid, and "[t]he definiteness inquiry focuses on whether those skilled in the art would understand the scope of the claim when the claim is read in light of the rest of the specification." *Union Pac. Resources Co.* v. *Chesapeake Energy Corp.*, 236 F.3d 684, 692 (Fed. Cir. 2001). Similarly, a patent must also contain a sufficient written description and must enable a practitioner to know how to practice it. *See* 35 U.S.C. § 112 ¶ 1 (claim must "contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same * * *"). These requirements ask whether the patent specification "allow[s] persons of ordinary skill in the art to recognize that the [inventor] invented what was claimed," *Gentry Gallery, Inc.* v. *Berline Corp.*, 134 F.3d 1473, 1479 (Fed. Cir. 1998), and "teach[es] those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech Inc.* v. *Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir.) (citation omitted), *cert. denied*, 522 U.S. 963 (1997).

A claim that simply directs a practitioner to "correlate" a test result with a medical condition fails all these tests and is therefore invalid. As the District Court correctly concluded, the "correlating" set forth in Claim 13 must "comprise a discrete, sequential process step." A221. But it has never been clear what the "correlating" step is—beyond a doctor simply thinking about the basic scientific association between elevated homocysteine levels and certain vitamin deficiencies. All the patent tells a prospective practitioner is that a person with an elevated homocysteine level *may* have a vitamin deficiency, which is simply a scientific fact. Such a claim is invalid for indefiniteness because one of ordinary skill in the art cannot determine its scope without specula-

tion.[15] Likewise, because neither the claim nor the specification describe what a practitioner must do to perform the active "correlating" step, it fails the written description and enablement requirements, for no one of skill in the art can tell, without undue experimentation, what the Claim 13 requires be done with the medical fact at issue.[16]

If the Court allows the Federal Circuit opinion to stand, anyone could obtain a patent on any scientific correlation—that there is a link between fact A and fact B—merely by drafting a patent claiming no more than "test for fact A and correlate with fact B," without any explanation of the testing or correlation processes. Claim 13 does no more than that. If the Federal Circuit decision is not corrected, CTI and others like it would improperly gain monopolies over basic scientific facts rather than any novel inventions of their own. As explained above, this Court's precedents are settled that no such claim can be allowed. *See supra* at 18.

As construed by the Federal Circuit, the correlating step does *not* require a doctor to actively perform any discrete

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[15] *See In re Steele*, 305 F.2d 859, 862-863 (C.C.P.A. 1962); *Honeywell Int'l, Inc.* v. *ITC*, 341 F.3d 1332, 1339 (Fed. Cir. 2003) (holding claim indefinite where patent claims and specification did not specify how to measure specific claimed parameter, and known methods produced varying results); *Union Pacific*, 236 F.3d at 692 (finding patent claim invalid for indefiniteness based on its use of the word "comparing").

[16] *See Lockwood* v. *American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1560-61 (Fed. Cir. 1991); *Union Pacific*, 236 F.3d at 688, 691 (affirming district court finding of patent invalidity when the patent lacked any explanation about *how* "correlating" was "achieved;" practitioners of the patent were thus left without adequate guidance on how to put the patent's teachings to use); *National Recovery Techs., Inc.* v. *Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1196-97 (Fed. Cir. 1999).

step in the patented process. *See* App. 8a (claim "only requires association of homocysteine levels with vitamin deficiencies. It requires no further correlation to confirm the relationship to vitamin deficiencies."); App. 12a ("the claim language does not require a confirmatory step linking these conditions to diagnosed or apparent symptoms"). But this Court's cases are clear that a method patent requires one to do something with a scientific fact. *See Funk Bros. Seed,* 333 U.S. at 130 ("He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes. If there is to be invention from such a discovery, it must come from the application of the law to a new and useful end."); *Mackay Radio & Tel.*, 306 U.S. at 94 ("While a scientific truth, or the mathematical expression of it, is not [a] patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be.").

Here, the patent as construed by the Federal Circuit tells practitioners merely that there is a scientific connection between elevated homocysteine and certain vitamin deficiencies. There is no further instruction as to what a practitioner must do to perform the "correlating" step. Under this Court's precedents, such an undefined claim cannot constitute a valid patented invention.

III. THIS CASE INVOLVES A QUESTION OF NATIONAL IMPORTANCE.

This case involves a question of extraordinary national importance. The Federal Circuit has held that one can gain a valid, legally protected patent monopoly over a basic scientific correlation such that any doctor who looks at test results and uses his or her medical knowledge just to *think* about what the result signifies has infringed the patent unless a license is granted and a royalty paid. And the Court went even further by holding that a third party that committed no direct infringement is nevertheless liable for induced infringement merely because it has disseminated that scientific

fact to doctors who may use it in diagnosing and treating patients. If this decision is allowed to stand, it will have grave adverse consequences for medical treatment throughout the Nation.

The patent laws appropriately protect new methods of testing for medical conditions. Thus, LabCorp has always recognized respondents' patent on the GCMS method for homocysteine tests and has always paid royalties when using that patented method. But what patent law cannot, and should not, protect are the medical facts that a test result may convey. *See supra* at 18. Protecting patented test methods encourages medical breakthroughs. But barring the disclosure of truthful medical knowledge prevents the medical profession from exercising appropriate medical judgment. Medical testing and treatment will be severely harmed if threats of patent lawsuits pressure doctors to delay or refrain from learning about medical facts that could help provide appropriate care and diagnosis.

The Federal Circuit's decision has cast precisely this kind of pall. The court upheld a patent claiming a right to prevent doctors from even *thinking* about a basic medical fact, holding that a doctor's mere speculation about the connection between homocysteine levels and vitamins constitutes the patented "correlating" step of Claim 13. And the court has held LabCorp liable for induced infringement—and enjoined it from directly performing any homocysteine tests under any method—merely because it has published this basic scientific fact. Respondents, moreover, have already shown that they are not stopping at LabCorp in their efforts to deter the performance of homocysteine tests. The very day the Federal Circuit's decision issued, respondent CTI filed a similar lawsuit against the *manufacturer* of a homocysteine test kit, accusing it of inducing infringement by doctors. *See Competitive Techs., Inc.* v. *Abbott Labs, Inc.*, No. 1:2004cv01169 (D. Colo.) (filed June 8, 2004). Two months later, CTI filed a second similar suit. *See Competitive Techs., Inc.* v. *Bayer*

Corp., No. 1:2004cv01712 (D. Colo.) (filed Aug. 17, 2004). And under respondents' and the Federal Circuit's view of the law, thousands of doctors are daily infringing the patent by "correlating" test results in their heads.

Single homocysteine tests are now critical to proper medical care and treatment in large part because of their utility in diagnosing increased risk of heart disease—the Nation's number one health problem. Indeed, the increased demand experienced by LabCorp occurred after the American Heart Association issued guidance to physicians informing them of the importance of homocysteine tests. *See* A8426. CTI itself has stated that "the size of the market could grow to *500 million assays* over the next five years." *See* Homocysteine Assay (http://www.competitivetech.net/technologies.htm#Homo); *see also* A7973-75, A7976-78 (1999 CTI press releases expressly linking elevated levels of homocysteine and heart disease, and noting that the number of tests was approaching approach 100 to 125 million tests per year). Yet according to the Federal Circuit, every doctor who orders one of these tests is infringing the Patent—no matter the method or reason for performing the test—unless CTI is paid a royalty. And unless the test has been licensed, any person who even informs a doctor of the basic scientific fact that elevated homocysteine is connected in some way to cobalamin or folate levels is guilty of induced infringement. Under the Federal Circuit's decision, doctors will now be deterred from treating patients, and other medical professionals will now be deterred from providing critical information needed for patient care.[17]

The importance of this case also extends far beyond the patent at issue. Under the Federal Circuit's holding, anyone

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[17] As noted above, homocysteine tests are useful for more than just screening for risk of heart disease. Elevated homocysteine levels have been associated with numerous other conditions ranging from lupus to Alzheimer's disease. *See supra* at 3.

who claims to be the first to discover a scientific correlation can patent that correlation—and thereby demand a royalty from anyone who even thinks about it—simply by drafting a vague "test plus correlate" claim. And that person could then prevent others from disseminating that patented scientific fact on the theory that such dissemination induces infringement. For example, someone who claims to have discovered the basic correlation between high cholesterol and heart disease risk could patent a two-step method: test for elevated cholesterol and "correlate" with risk of heart disease. The hypothetical patentee then could prevent doctors from ordering any cholesterol tests and prevent anyone else—including professors or authors of medical textbooks—from informing doctors about the basic correlation. Literally *any* scientific "correlation" could be patented in such a matter, thereby employing the patent laws to stifle rather than encourage the dissemination of scientific knowledge.

LabCorp was held liable in this case because it published a medical fact useful in the treatment of patients, and for no other reason. Medical facts, like all scientific principles and laws of nature, belong to the public. Medical professionals and others must be able to discuss such facts—including the correlation at issue here—without fear of liability for infringing or inducing another to infringe a patent. The Federal Circuit's decision in this case thus threatens to hinder the free and open dissemination of critical medical information. Indeed, the American Heart Association presently publishes on its website truthful information about homocysteine and vitamins that is identical in all relevant respects to the statements for which LabCorp was held liable for inducing infringement.[18] Under the Federal Circuit's holding, these

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[18] The American Heart Association's website currently provides the following information:

> Homocysteine is an amino acid in the blood. Too much of it is related to a higher risk of coronary heart disease, stroke and peripheral vascular disease (fatty deposits in peripheral

kinds of statements from medical professionals, and others like them, could well lead to crippling liability.

Although LabCorp is the party that bears the judgment in this case, if the Federal Circuit's decision is not reversed the ultimate losers will be thousands of doctors and millions of their patients. The Court should therefore grant review to clarify that the patent laws do not permit a party to gain a monopoly over the thought processes of doctors or prevent anyone from simply disseminating truthful information about a basic scientific fact critical to patient care.

CONCLUSION

For the foregoing reasons, the petition should be granted and the judgment below reversed.

JOHN P. HIGGINS
ALSTON & BIRD, LLP
Bank of America Plaza
101 South Tryon Street
Suite 4000
Charlotte, NC 28280
(704) 444-1000

* Counsel of Record

JONATHAN S. FRANKLIN*
CATHERINE E. STETSON
JESSICA L. ELLSWORTH
HOGAN & HARTSON L.L.P.
555 Thirteenth Street, N.W.
Washington, D.C. 20004
(202) 637-5766

Counsel for Petitioner

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arteries). * * * Folic acid and other B vitamins help break down homocysteine in the body. * * * [P]atients at high risk should be strongly advised to be sure to get enough folic acid and vitamins B-6 and B-12 in their diet.

Homocysteine, Folic Acid and Cardiovascular Disease (www.americanheart.org/presenter.jhtml?identifier=4677).

APPENDIX

APPENDIX A

United States Court of Appeals for the Federal Circuit

03-1120

METABOLITE LABORATORIES, INC.
and COMPETITIVE TECHNOLOGIES, INC.,

Plaintiffs-Appellees,

v.

LABORATORY CORPORATION OF AMERICA
HOLDINGS
(doing business as LabCorp),

Defendant-Appellant.

Glenn K. Beaton, Gibson, Dunn & Crutcher LLP, of Denver, Colorado, argued for plaintiffs-appellees. With him on the brief were *J. Gregory Whitehair* and *Amanda J. Tessar*. Also on the brief was *Mark A. Perry*, of Washington, DC.

Jonathan S. Franklin, Hogan & Hartson L.L.P., of Washington, DC, argued for defendant-appellant. With him on the brief was *Catherine E. Stetson*. Of counsel on the brief was *John P. Higgins*, Alston & Bird, LLP, of Charlotte, North Carolina.

Appealed from: United States District Court for the District of Colorado

Senior Judge Zita L. Weinshienk

DECIDED: June 8, 2004

BEFORE RADER, Circuit Judge, FRIEDMAN, Senior Circuit Judge, and SCHALL, Circuit Judge.

Opinion for the court filed by *Circuit Judge* RADER, dissenting-in-part and concurring-in-part opinion filed by *Circuit Judge* SCHALL. RADER, *Circuit Judge*.

In the United States District Court for the District of Colorado, a jury found that Laboratory Corporation (LabCorp) indirectly infringed Metabolite Laboratories, Inc.'s (Metabolite's) U.S. Patent No. 4,940,658 (the '658 patent). The jury also found that LabCorp partially breached its contract with Metabolite. Based on this verdict, the district court assessed damages of $3,652,724.61 for breach of contract and $1,019,365.01 for indirect infringement. *Metabolite Labs., Inc.* v. *Lab. Corp.*, No. 99-Z-870 (D. Colo. Dec. 3, 2001). After denying LabCorp's motion for judgment as a matter of law (JMOL), the district court doubled the infringement award for willful infringement and issued a permanent injunction. *Metabolite Labs., Inc.* v. *Lab. Corp.*, No. 99-Z-870 (D. Colo. Nov. 19, 2001). Because the record supports the jury's verdicts and the trial court's decisions, this court affirms.

I.

The '658 patent claims methods for detecting cobalamin or folate deficiency. Cobalamin and folate are both B vitamins, commonly known as B_{12} and folic acid, respectively. A deficiency in these vitamins can cause serious illnesses in humans, including vascular disease, cognitive dysfunction, birth defects and cancer. If detected early enough, however, vitamin supplements readily treat the deficiency.

Because these B vitamins assist in metabolizing the amino acid homocysteine, scientists directly assayed homocysteine to screen for cobalamin and folate deficiency. These direct homocysteine assays were unreliable. Then researchers at University Patents Inc. (UPI) discovered a relationship between elevated levels of total homocysteine and a deficiency in either cobalamin or folate. The total homocysteine

test, however, could not alone identify which vitamin was deficient. Total homocysteine includes free and protein-complexed homocysteine and also includes homocysteine derivatives homocystine and homocysteine-cysteine.

Originally, doctors could not conveniently treat both deficiencies because while folate was available in tablet form, cobalamin could only be administered by injection. After cobalamin became available in tablet form, however, doctors could simply order a total homocysteine test and, without identifying the deficient vitamin, treat elevated levels of total homocysteine with a tablet containing both cobalamin and folate. The UPI inventors also developed a test to identify the deficient vitamin using methylmalonic acid (the panel test method). The '658 patent claims both the total homocysteine test and the total homocysteine-methylmalonic acid test.

Claim 13 claims the total homocysteine test:

> 13. A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> assaying a body fluid for an elevated level of total homocysteine; and
>
> correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

'658 patent, col. 11, ll. 58-65.

UPI's successor, Competitive Technologies Inc., licensed the patent to Metabolite, which in turn sublicensed the patent to Roche Biomedical Laboratories (now LabCorp). LabCorp, a laboratory testing company, originally performed total homocysteine assays under the sublicense. But in 1998, LabCorp switched to a total homocysteine assay developed by Abbott Laboratories (Abbott test) and discontinued royalty payments to Metabolite for total homocysteine assays.

In response, Metabolite sued LabCorp for infringement. The district court construed the disputed claim terms, and the case proceeded to a jury. The jury found that LabCorp

breached its license agreement with Metabolite, that LabCorp willfully infringed the '658 patent, and that the claims at issue are not invalid. The jury assessed damages against LabCorp of $3,652,724.61 for breach of contract and $1,019,365.01 for infringement. The district court entered judgment against LabCorp and awarded damages as assessed by the jury.

After the trial, the district court denied LabCorp's motion for JMOL on infringement, breach of contract, invalidity, and willful infringement. In light of the finding of willfulness, the district court doubled the jury's infringement award to $2,038,730.02. The district court also permanently enjoined LabCorp from using the homocysteine-only test. LabCorp appeals the district court's claim construction as well as the denial of JMOL.

II.

Claim construction is a matter of law that this court reviews without deference. *Cybor Corp.* v. *FAS Techs., Inc.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998) (en banc). The jury's finding of infringement, however, raises questions of fact, which this court reviews for substantial evidence. *Embrex, Inc.* v. *Serv. Eng'g Corp.*, 216 F.3d 1343, 1348-49 (Fed. Cir. 2000).

This court reviews a denial of JMOL without deference by reapplying the JMOL standard. Thus, this court will affirm a denial of JMOL unless substantial evidence does not support the jury's factual findings or the verdict rests on legal errors. *Waner* v. *Ford Motor Co.*, 331 F.3d 851, 855 (Fed. Cir. 2003).

Whether a specification complies with the written description requirement of 35 U.S.C. § 112, paragraph 1, is a question of fact that this court reviews for substantial evidence. *Union Oil* v. *Atl. Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000). Enablement is a matter of law that this court reviews without deference; however, this court reviews the factual underpinnings of enablement for substantial

evidence. *BJ Servs. Co.* v. *Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1371-72 (Fed. Cir. 2003). Similarly, this court reviews the legal determination of obviousness without deference, but reviews its factual underpinnings for substantial evidence. *Teleflex, Inc.* v. *Ficosa N. Am. Corp.*, 299 F.3d 1313, 1323 (Fed. Cir. 2002). This court reviews a legal finding of indefiniteness without deference. *BJ Servs.*, 338 F.3d at 1371-72. Whether a prior art reference anticipates a patent is a factual determination that this court reviews for substantial evidence. *Teleflex*, 299 F.3d at 1323.

Whether infringement was willful is a question of fact that this court reviews for substantial evidence. *Crystal Semiconductor Corp.* v. *TriTech Microelecs. Int'l, Inc.*, 246 F.3d 1336, 1346 (Fed. Cir. 2001). This court reviews an award of enhanced damages and grant of a permanent injunction for abuse of discretion. *Odetics, Inc.* v. *Storage Tech. Corp.*, 185 F.3d 1259, 1272 (Fed. Cir. 1999).

III.

Infringement

The primary challenge to the jury's indirect infringement verdict requires this court to review the district court's construction of the claim term "correlating." The infringement inquiry is a two-step process. This court construes the disputed claim terms and then compares the properly construed claims to the accused device. *Cybor Corp.*, 138 F.3d at 1454. Thus, this court first reviews the district court's claim construction.

As always, the claim language itself governs its meaning. *Vitronics Corp.* v. *Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). This court construes the meaning of claim language according to its usage and context. *ResQNet.com, Inc.* v. *Lansa, Inc.*, 346 F.3d 1374, 1378 (Fed. Cir. 2003). The touchstone for discerning the usage of claim language is the understanding of those terms among artisans of ordinary skill in the relevant art at the time of invention. *See Rexnord Corp.* v. *Laitram Corp.*, 274 F.3d 1336, 1342 (Fed. Cir.

2001). Indeed, normal rules of usage create a "heavy presumption" that claim terms carry their accustomed meaning in the relevant community at the relevant time. *CCS Fitness, Inc.* v. *Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002) (citing *Johnson Worldwide Assocs., Inc.* v. *Zebco Corp.*, 175 F.3d 985, 989 (Fed. Cir. 1999)). Thus, this court sets the meaning of claim terms by ascertaining their technological and temporal context.

In most cases, the best source for discerning the proper context of claim terms is the patent specification wherein the patent applicant describes the invention. In addition to providing contemporaneous technological context for defining claim terms, the patent applicant may also define a claim term in the specification "in a manner inconsistent with its ordinary meaning." *Boehringer Ingelheim Vetmedica, Inc.* v. *Schering-Plough Corp.*, 320 F.3d 1339, 1347 (Fed. Cir. 2003) (citing *Teleflex*, 299 F.3d at 1325-26). In other words, a patent applicant may define a term differently from its general usage in the relevant community, and thus expand or limit the scope of the term in the context of the patent claims. *Id.* Therefore, the primary aids to supply the context for interpretation of disputed claim terms are in the intrinsic record. *Vitronics*, 90 F.3d at 1582 (Fed. Cir. 1996).

Another tool to supply proper context for claim construction is the prosecution history. As in the case of the specification, the patent applicant's consistent usage of a term in prosecuting the patent may enlighten the meaning of that term. *Middleton, Inc.* v. *Minn. Mining & Mfg. Co.*, 311 F.3d 1384, 1388 (Fed. Cir. 2002) (a patent applicant may "clearly and unambiguously" disavow claim scope during prosecution).

This court also acknowledges the relevance of extrinsic evidence, often presented in the form of expert testimony. *Pitney Bowes, Inc.* v. *Hewlett-Packard Co.*, 182 F.3d 1298, 1309 (Fed. Cir. 1999) ("[C]onsultation of extrinsic evidence is particularly appropriate to ensure that [the court's]

understanding of the technical aspects of the patent is not entirely at variance with the understanding of one skilled in the art."); *Vitronics*, 90 F.3d at 1585. Another excellent source of context for disputed terms is dictionary definitions and treatises. *See, e.g., Tex. Digital Sys., Inc.* v. *Telegenix, Inc.*, 308 F.3d 1193, 1202 (Fed. Cir. 2002) ("[D]ictionaries, encyclopedias and treatises are particularly useful resources to assist the court in determining the ordinary and customary meanings of claim terms.").

As noted before, these claim construction aids inform the court's task of ascertaining the meaning of the claim terms to one of ordinary skill in the art at the time of invention. *Moba* v. *Diamond Automation, Inc.*, 325 F.3d 1306, 1315 (Fed. Cir. 2003) ("Moreover, as this court has repeatedly counseled, the best indicator of claim meaning is its usage in context as understood by one of skill in the art at the time of invention."); *Ferguson Beauregard* v. *Mega Sys., LLC*, 350 F.3d 1327, 1338 (Fed. Cir. 2003) ("The words used in the claims must be considered in context and are examined through the viewing glass of a person skilled in the art."); *Interactive Gift Express, Inc.* v. *Compuserve Inc.*, 256 F.3d 1323, 1332 (Fed. Cir. 2001) ("[I]t is important to bear in mind that the viewing glass through which the claims are construed is that of a person skilled in the art."); *Markman* v. *Westview Instruments, Inc.*, 52 F.3d 967, 986 (Fed. Cir. 1995) (en banc) ("[T]he focus is on the objective test of what one of ordinary skill in the art at the time of the invention would have understood the term to mean."). In this case, as evidenced by the jury instruction, the parties agreed that the level of ordinary skill in this field of invention was "a person having a medical degree and experience in researching the amino acid homocysteine and its relationship to diseases."

The disputed term "correlating" appears in the second step of claim 13, which states: "[C]orrelating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate." In its *Markman* brief below, LabCorp

urged the district court to construe "correlate" according to its dictionary definition as a verb meaning "to establish a mutual or reciprocal relation of" an elevated level of homocysteine. LabCorp further argued that the district court should construe the "correlating" step as establishing that an elevated level of homocysteine is caused by a "shortage of cobalamin which causes a hematologic or neuropyschiatric abnormality," or "[a] deficiency of folate which causes a hematologic abnormality." The district court adopted LabCorp's dictionary definition by construing "correlating" to mean "to establish a mutual or reciprocal relationship between," but declined to "include a reference to hematologic or neuropsychiatric abnormality" in order to avoid impermissibly importing a limitation from the specification.

On appeal, LabCorp argues that claim 13's correlating step should be construed as establishing that an elevated level of homocysteine is caused by a "shortage of cobalamin which causes a hematologic or neuropsychiatric abnormality," or a "deficiency of folate which causes a hematologic abnormality." LabCorp interprets the specification to clearly define a "deficiency of cobalamin" as the presence of a clinical or hematologic syndrome or both that responds to cyano-cobalamin treatment, and to acknowledge that some clinical or hematologic syndrome or neuropsychiatric abnormality must be present. Thus, LabCorp contends that the correlation step of claim 13 should be construed to require a showing of a separate hematologic or neuropsychiatric symptom to confirm the "correlation."

The claim states that the method must correlate "an elevated level of total homocysteine . . . with a deficiency of cobalamin or folate." This language does not require a further association between the level of total homocysteine and either a hematologic or neuropyschiatric abnormality or both. The claim only requires association of homocysteine levels with vitamin deficiencies. It requires no further correlation to confirm the relationship to vitamin deficiencies. The

claim simply says nothing about a confirmatory step or a further correlation beyond the stated relationship.

The preamble further supports the district court's reading of the claim: "A method for detecting a deficiency of cobalamin or folate in warm-blooded animals." This language restates that the invention detects vitamin deficiency. This introductory language does not relate those deficiencies to any particular abnormality. A preamble may provide context for claim construction, particularly, where as here, that preamble's statement of intended use forms the basis for distinguishing the prior art in the patent's prosecution history. *Catalina Mktg. Int'l, Inc.* v. *Coolsavings.com, Inc.*, 289 F.3d 801, 809 (Fed. Cir. 2002) (in rare circumstances, a preamble's recitation of intended use may serve to distinguish the prior art).

An examination of the prosecution history of this patent brings the meaning of the preamble into focus. As originally filed, claim 13 did not contain the "correlating" step. The examiner rejected claim 13 under 35 U.S.C. § 112 because it did not "recite discrete, sequential process steps, for example, obtaining a sample, contacting the sample with, etc. The final step should be clearly related to the preamble of the claim." Rather than add a second step as the examiner suggested, however, the applicant responded: "[A]s applicants are the first to detect cobalamin or folate deficiency by assaying body fluids for total homocysteine, it is believed that they are entitled to a claim of equivalent scope, not limited to any particular steps or methods." After this response, the examiner dropped the § 112 objection, but rejected claim 13 under § 102: "In the absence of a correlation step, the preamble of claim 13 merely recites an intended use of the invention. The claim lacks a positive limitation for correlating to a particular condition and has only one method step recited." At that point, the applicant added the recommended "correlating" step. The examiner then allowed claim 13.

This prosecution history ties the preamble directly to the "correlating" step. Specifically, the recitation of the intended use in the preamble makes this invention a method for detecting a vitamin deficiency. "Detecting" in the medical context requires evaluation of all test results, both positive and negative, to evaluate a patient's condition. For example, the results of a pregnancy test can either be positive or negative. Either result is informative to the patient. Similarly, in this case, the assaying step can identify an elevated or an unelevated level of total homocysteine. Then the "correlating" step can identify, in cases of elevated levels, a relationship or not to vitamin deficiency. The results in either the assaying or correlating steps are informative. Thus, the preamble supports the district court's construction that "correlating" includes ascertaining either a mutual or reciprocal relationship between total homocysteine and a vitamin deficiency. The preamble does not require this invention to show a further association with an abnormality.

The specification confirms that the claim language does not require as part of the method a confirmation that the elevated level causes some deleterious symptoms or abnormalities. LabCorp points to portions of the specification that discuss the relationship between the elevated levels and either clinical or hematologic symptoms. *See, e.g.*, '658 patent, col. 10, ll. 56-61; col. 12, ll. 8-15. LabCorp would expand those references to require some confirmatory step in the claim. The specification, however, does not require such a confirmatory step. Rather, the specification at one juncture acknowledges that the method can show vitamin deficiency without any clinical symptoms: "These findings led us to conclude that large numbers of patients with cobalamin deficiency lack the 'typical' clinical and hematologic features usually expected to be present in cobalamin deficiency . . . ." *Id.* at col. 11, ll. 40-45. In other words, the specification shows that the method can show an association between elevated levels and vitamin deficiency without any further clinical symptoms. Thus, the district court properly refused

to import into the claims LabCorp's proposed limitation from the specification. The specification itself does not support such a limitation on the meaning of the claims.

As noted earlier, the district court construed "correlating" to mean a "mutual or reciprocal relationship between" the elevated levels and the vitamin deficiencies. The inventors discovered that assaying total homocysteine correlated with (or predicted relatively accurately) whether a patient had a deficiency of cobalamin or folate. *Id.* at col. 4. ll. 17-23; col. 10, ll. 35-42. The specification explains that an elevated level of total homocysteine often indicates a deficiency, while a non-elevated level indicates no deficiency. For example, the overview of the invention notes: "This invention pertains to . . . methods for determining whether said warm-blooded animal has a cobalamin deficiency, a folic acid deficiency, *neither*, or both." *Id.* at col. 1, ll. 13-15 (emphasis added). Next, in the summary of the invention, the patentee stated: "Accordingly, assays for homocysteine can be used to determine the *presence or absence* of cobalamin and/or folic acid deficiency in warm-blooded animals." *Id.* at col. 5, l. 66 - col. 6, l. 1 (emphasis added). This court observes that the perfect symmetry between "mutual or reciprocal" and "presence or absence" shows that the district court correctly placed the term "correlating" in its proper context with its proper meaning.

Finally, the patentee explained:

> Once folate and/or cobalamin deficiency has been determined, the progress of treatment can be monitored by repeating the assays periodically during and after treatment. A drop in the level of homocysteine in the serum and/or urine after oral or parenteral adminstration of cobalamin and/or folate as the case may be confirms the diagnosis.

Id. at col. 10, ll. 18-24. This recitation confirms that the patentee anticipated assays without an elevated level of total homocysteine, i.e., the reciprocal relationship, would further

confirm the diagnosis by showing an improvement trend after a physician prescribed treatment.

Taken in the context of the entire specification, "correlating" means relating total homocysteine levels to cobalamin or folate deficiency, a deficiency in both, or a deficiency in neither. In essence, "correlating" means to relate the presence of an elevated total homocysteine level to either a cobalamin or folate deficiency, or both (i.e., a mutual relationship), and also to relate the absence of an elevated total homocysteine level to a deficiency in neither (i.e., a reciprocal relationship). The claim, in other words, provides that if the assay discloses "an elevated level of total homocysteine," the physician determines whether there is a cobalamin or folate deficiency by "correlating," i.e., comparing the elevated level with the normal homocysteine level. In sum, the specification and prosecution history confirm that the claim language "correlating," in the understanding of one of ordinary skill in this art field at the time of invention, includes both a mutual relationship between the presence of an elevated level of homocysteine and a vitamin deficiency and a reciprocal relationship between the absence of an elevated level of homocysteine and no vitamin deficiency. Further, the claim language does not require a confirmatory step linking these conditions to diagnosed or apparent symptoms. The district court correctly construed the claim.

LabCorp also raises claim construction arguments in its challenge to the trial court's assessment of damages. Specifically, LabCorp contends that only twenty percent of the assays have elevated levels of homocysteine and therefore only this percentage could form the basis for a damages award. As noted earlier, LabCorp itself urged the district court to define "correlating" to include either a mutual or a reciprocal relationship. In the damages calculation, however, LabCorp prefers to restrict the claim to correlations that yield mutual relationships while excluding any reciprocal relationships. This court declines the

invitation to apply a different claim construction for computation of damages than for infringement liability.

As explained above, the mutual relationship is established when an elevated homocysteine level is present, whereas a reciprocal relationship is established when an elevated homocysteine level is absent. LabCorp's new damages argument, in essence, attempts to change its claim construction position to read out the reciprocal relationship that it initially urged. This court, as it does now, has previously declined such invitations. Interactive Gift Express, 256 F.3d at 1346 (Fed. Cir. 2001) ("[A] party will be judicially estopped from asserting a position on appeal that is inconsistent with a position it advocated at trial and persuaded the trial court to adopt."). For all purposes in this litigation, this court affirms the district court's construction of the "correlating" step.

Direct Infringement

The jury found LabCorp liable for indirect infringement. The record must show the presence of direct infringement, however, to support the verdict of indirect infringement. *Joy Techs., Inc.* v. *Flakt, Inc.*, 6 F.3d 770, 774 (Fed. Cir. 1993) ("Liability for either active inducement of infringement or for contributory infringement is dependent upon the existence of direct infringement."). Thus, this court must examine whether there is substantial evidence in the record of the physicians' direct infringement. In that respect, the parties hinge the direct infringement issue solely on whether the physicians perform the correlating step.[1] Hence, we review the record for substantial evidence of that step.

Substantial evidence supports the jury's verdict. The record shows that physicians order assays and correlate the results of those assays, thereby directly infringing. LabCorp's Discipline Director, Dr. Peter Wentz, testified that the physicians receiving total homocysteine assays from

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[1] This court, therefore, does not address the assaying step.

LabCorp carry out the correlating step.[2] Specifically, Dr. Wentz testified that "the correlating step . . . [is] a separate, distinct step that's performed by the physician who receives . . . our results." Inventor Dr. Sally Stabler also testified that it would be malpractice for a doctor to receive a total homocysteine assay without determining cobalamin/folate deficiency.

To support the verdict, the record does not need to contain direct evidence that every physician performed the "correlating" step. "It is hornbook law that direct evidence of a fact is not necessary. 'Circumstantial evidence is not only sufficient, but may also be more certain, satisfying and persuasive than direct evidence.'" *Moleculon Research Corp.* v. *CBS, Inc.*, 793 F.2d 1261, 1272 (Fed. Cir. 1986) (citing *Michalic* v. *Cleveland Tankers, Inc.*, 364 U.S. 325, 330 (1960)). As discussed above, the record contains sufficient circumstantial evidence to permit the jury to imply that physicians directly infringe.

Active Inducement

Section 271(b) of title 35 provides: "Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b) (2000). Although not express in the statute, this section requires proof of intent to induce infringement. *See, e.g., Hewlett Packard Co.* v. *Bausch & Lomb Inc.*, 909 F.2d 1464, 1469 (Fed. Cir. 1990) ("proof of actual intent to cause the acts which constitute the infringement is a necessary prerequisite to finding active inducement"). A patentee may prove such intent through circumstantial evidence, much like direct infringement as discussed above. *See Water Techs.* v. *Calco, Ltd.*, 850 F.2d 660, 668 (Fed. Cir. 1988) (noting that "circumstantial evidence may suffice" in proving intent).

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[2] Peter Wentz has a doctoral, not a medical, degree.

The record contains such evidence of intent. LabCorp's own publications supply much of this evidence. LabCorp publishes both Continuing Medical Education articles as well as a Directory of Services that are specifically targeted to the medical doctors ordering the LabCorp assays. These publications state that elevated total homocysteine correlates to cobalamin/folate deficiency and that this deficiency can be treated with vitamin supplements. LabCorp's articles thus promote total homocysteine assays for detecting cobalamin/folate deficiency.

Faced with these statements, LabCorp attempts to explain that these articles focus on heart disease rather than vitamin deficiency. As noted earlier, the patent does not require a correlation to some particular medical condition, but to a vitamin deficiency. The publications advocate use of the assay to identify a need for cobalamin/folate supplements. Thus, the vitamin deficiency remains the focus of the assay and the treatment (i.e., vitamin supplements).

Accordingly, a reasonable jury could find intent to induce infringement because LabCorp's articles state that elevated total homocysteine correlates to cobalamin/folate deficiency. Moreover, the publications recommend treatment of this deficiency with vitamin supplements. Because "[i]ntent is a factual determination particularly within the province of the trier of fact," *Allen Organ Co.* v. *Kimball Int'l, Inc.*, 839 F.2d 1556, 1557 (Fed. Cir. 1988), this court sees no reason to disturb the jury's finding regarding LabCorp's intent. Therefore, this court affirms the finding of indirect infringement based on the inducement analysis. This court declines to consider contributory infringement.

Invalidity

A patent issued from the United States Patent and Trademark Office (PTO) bears the presumption of validity under 35 U.S.C. § 282. An accused infringer, therefore, must prove patent invalidity under the clear and convincing evidentiary standard. *Advanced Display Sys., Inc.* v. *Kent State*

Univ., 212 F.3d 1272 (Fed. Cir. 2000). LabCorp argues that claim 13 is invalid on grounds of indefiniteness, lack of written description and enablement, anticipation, and obviousness. Likewise, LabCorp contends that claim 18, directed to the panel test, is also invalid on grounds of indefiniteness, and lack of written description and enablement.

Claim 13

First, LabCorp contends that the "correlating" step in claim 13 is indefinite. 35 U.S.C. § 112, second paragraph, provides: "The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112, ¶ 2 (2000). The requirement to "distinctly" claim means that the claim must have a meaning discernible to one of ordinary skill in the art when construed according to correct principles. *Union Pac. Res. Co.* v. *Chesapeake Energy Corp.*, 236 F.3d 684, 692 (Fed. Cir. 2001); *Rosemount, Inc.* v. *Beckman Instruments, Inc.*, 727 F.2d 1540, 1547 (Fed. Cir. 1984). Only when a claim remains insolubly ambiguous without a discernible meaning after all reasonable attempts at construction must a court declare it indefinite. *Exxon Research & Eng'g Co.* v. *United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001). In this case, as already noted, the claim construction exercise at the trial court produced a discernible and clear meaning. No "material ambiguities" cloud the meaning of "correlating" to the extent that one of skill in the art would find the claim wholly indefinite. *All Dental Prodx, LLC* v. *Advantage Dental Prods., Inc.*, 309 F.3d 774, 780 (Fed. Cir. 2002) ("Only after a thorough attempt to understand the meaning of a claim has failed to resolve material ambiguities can one conclude that the claim is invalid for indefiniteness."). This court affirms the trial court's denial of JMOL on this ground.

LabCorp next argues that the specification does not adequately describe the claimed invention under 35 U.S.C. § 112, first paragraph:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the same . . . .

35 U.S.C. § 112, ¶ 1. This language contains both the written description and enablement tests for sufficiency of the specification's disclosure.

With regard to the written description test, this court has previously explained, "the test for compliance with § 112 has always required sufficient information in the original disclosure to show that the inventor possessed the invention at the time of the original filing." *Moba*, 325 F.3d at 1320 (citing *Vas-Cath Inc.* v. *Mahurkar*, 935 F.2d 1555, 1561 (Fed. Cir. 1991)). As in the claim construction section above, this court assesses the written description possession test "from the viewpoint of one of skill in the art." *Moba*, 325 F.3d at 1321. The record is replete with evidentiary support that physicians in homocysteine research, i.e., persons of ordinary skill in the art, understood from the specification that the '658 patent inventors possessed the "correlating" step at the time they filed the patent application. For example, the examiner suggested the word "correlating" to the '658 patentee, showing that the PTO read the specification to include that feature. Additionally, the record reflects that LabCorp's own expert and employees understood the meaning of "correlating." Accordingly, this court finds that substantial evidence supports the jury finding that claim 13 was adequately supported by the '658 patent's written description.

The specification also shows that the patentee enabled the claimed invention. In *Union Pacific*, this court held that a claim was not enabled because it did not disclose use of a "comparing" step. 236 F.3d at 691. However, in *Union Pacific*, the inventors "purposely excluded computer programming details" necessary to perform the "comparing"

step. *Id.* at 690. In this case, the correlating step does not require computer technology or extensive computations. Instead, the record shows repeatedly that the correlating step is well within the knowledge of one of skill in this art. The correlating step is a simple conclusion that a cobalamin/folate deficiency exists *vel non* based on the assaying step. The patentee did not conceal or fail to disclose this correlation, but instead featured it as the centerpiece of the invention. *See, e.g.*, '658 patent, col. 4, ll. 17-20 ("It has now been discovered that an elevated level of total homocysteine in tissues of warmblooded [sic] animals correlates both with cobalamin deficiency and with folic acid deficiency . . . ."); *id.* at col. 5, ll. 64-66 ("It has been discovered that elevated levels of homocysteine in body tissue correlate with decreased levels of cobalamin and/or folic acid in said body tissue."); *id.* at col. 9, ll. 26-29 ("Homocysteine levels above these [previously specified] ranges are indicative of cobalamin and/or folate deficiency; the higher the level, the stronger the indication.").

The prior art reference (Refsum) does not anticipate claim 13 under 35 U.S.C. § 102. "A prior art reference anticipates a patent claim if the reference discloses, either expressly or inherently, all of the limitations of the claim." *EMI Group N. Am., Inc.* v. *Cypress Semiconductor Corp.*, 268 F.3d 1342, 1350 (Fed. Cir. 2001) (citation omitted). At the outset, the Refsum article does not recite all of the claim 13 limitations. Thus, anticipation would have to rely on an inherent disclosure of undisclosed features, in this case, the "correlating" limitation.

> To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.

Continental Can Co. v. *Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991).

Refsum does disclose that total homocysteine should be used to investigate "perturbations of homocysteine metabolism in humans during disease or pharmacological interventions that affect metabolism of one-carbon compounds." Refsum, however, does not specifically mention cobalamin or folate deficiencies. Indeed, one of the '658 patent inventors, Dr. Stabler, testified that cobalamin and folate deficiencies constitute just such a perturbation that Refsum suggested warranted further investigation. Rather than necessarily containing the correlation between homocysteine and cobalamin or folate deficiencies, Refsum simply invites further experimentation to find such associations. An invitation to investigate is not an inherent disclosure. Construed most favorably for LabCorp, Refsum discloses no more than a broad genus of potential applications of its discoveries. A prior art reference that discloses a genus still does not inherently disclose all species within that broad category. *See Corning Glass Works* v. *Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1262 (Fed. Cir. 1989) ("Under [defendant's] theory, a claim to a genus would inherently disclose all species. We find [this] argument wholly meritless . . . .").

Moreover, the PTO considered Refsum in allowing the claims. The '658 patent itself discusses Refsum at length at column 6, lines 26-43 and the patent's second page cites Refsum as a reference. Where, as here, the PTO previously considered the prior art reference, LabCorp bears an even heavier burden to prove invalidity. *Hewlett-Packard*, 909 F.2d at 1467. ("This burden is especially difficult when the prior art was before the PTO examiner during prosecution of the application." (citation omitted)). Accordingly, substantial evidence supports the jury's finding that Refsum does not anticipate claim 13 by inherency.

The test of obviousness in 35 U.S.C. § 103 is the primary condition of patentability. Obviousness hinges on four factual findings: "(1) the scope and content of the prior art; (2) the differences between the prior art and the claims; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness." *Nat'l Steel Car, Ltd.*, v. *Can. Pac. Ry., Ltd.*, 357 F.3d 1319, 1334 (Fed. Cir. 2004). LabCorp posits that claim 13 is obvious in view of the Refsum article when combined with other references disclosing that partial homocysteine assays could help diagnose cobalamin or folate deficiency. First, as noted above in the anticipation analysis, the examiner considered the Refsum article and also considered all but one of the secondary references that LabCorp contends render the invention obvious in combination with Refsum. The one reference that the examiner did not consider is cumulative of the others. Thus, the heavy burden of proof in the anticipation case also applies to obviousness. *Hewlett-Packard*, 909 F.2d at 1467. Next, the secondary references do not refer to total homocysteine, but rather to homocystine, one of the four components of total homocysteine. Thus, these secondary references do not add considerably to the Refsum disclosure. Finally, even if the secondary references disclosed total homocysteine, the record does not contain evidence showing that one of skill in the art would have been motivated to combine the various references. *Ecolochem, Inc.* v. *S. Cal. Edison Co.*, 227 F.3d 1361, 1372 (Fed. Cir. 2000) ("Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination." (quoting *ACS Hosp. Sys., Inc.* v. *Montefiore Hosp.*, 732 F.2d 1572, 1577 (Fed. Cir. 1984))). These points alone would suffice to support the jury verdict.

Beyond these points, however, the record contains evidence of objective indicia that support the jury's nonobviousness verdict. The record, for example, shows that skilled artisans were initially skeptical about the invention.

See Hughes Tool Co. v. *Dresser Indus., Inc.*, 816 F.2d 1549, 1556 (Fed. Cir. 1987) (initial skepticism of experts is relevant to nonobviousness). The record also shows that Metabolite has licensed the invention to eight companies. *In re Sernaker*, 702 F.2d 989, 996 (Fed. Cir. 1983) (extensive licensing supports nonobviousness). Substantial evidence, therefore, supports the implied jury factual findings that support its legal conclusion that claim 13 is not obvious in light of the Refsum article and the cited secondary references.

In sum, this court rejects LabCorp's various attempts to invalidate claim 13. Accordingly, this court affirms the district court's denial of LabCorp's JMOL.

Claim 18

Unlike claim 13, which Metabolite specifically asserted in its motion for partial summary judgment, Metabolite also requested the district court to declare that claim 18 covers the panel test method. Specifically, Metabolite sought a declaration that LabCorp's panel test that determines which particular vitamin is deficient infringes claim 18. The district court granted Metabolite's motion for partial summary judgment, finding that "[c]laim 18 covers LabCorp's performance of the panel test." In turn, LabCorp challenged the validity of claim 18 at trial. Neither party disputes that LabCorp continues to pay royalties for the panel test that provides the capability to identify which of the two vitamins is deficient.

Before this court can reach the merits of LabCorp's validity challenge, however, it must first ascertain whether it has jurisdiction to consider this challenge. Subject matter jurisdiction is an inquiry that this court must raise *sua sponte*, even where, as here, neither party has raised this issue. *Textile Prods., Inc.*, v. *Mead Corp.*, 134 F.3d 1481, 1485 (Fed. Cir. 1998) ("Every federal appellate court has a special obligation to 'satisfy itself not only of its own jurisdiction, but also that of the lower courts in a cause under review,' even though the

parties are prepared to concede it." (quotation omitted)); *see also Gen-Probe Inc.* v. *Vysis, Inc.*, 359 F.3d 1376, 1379 (Fed. Cir. 2004) ("Any party or this court *sua sponte* may raise the question of subject matter jurisdiction.").

Although not as common as the scenario in which the alleged infringer seeks declaratory judgment against the patentee, it is possible for a patentee to also seek a declaratory judgment against a future infringer. *See Lang* v. *Pac. Marine & Supply Co., LTD.*, 895 F.2d 761, 763 (Fed. Cir. 1990) (noting that patentees seeking declaratory judgments against future infringers are rare, yet permissible). In order to demonstrate that an actual case or controversy exists, however, a patentee must demonstrate two elements. First, the patentee must show that the future infringer is "engaged in an activity directed to making, selling, or using subject to an infringement charge under 35 U.S.C. § 271(a)." *Lang*, 895 F.2d at 764. The patentee must then demonstrate that the defendant's acts represent a refusal to alter its course of action in light of the patentee's warning actions. *Id.*

The facts of this case, however, demonstrate that there is no real case or controversy regarding the LabCorp panel test, alleged to infringe claim 18. Neither party disputes that the license is still in effect as to the panel tests that LabCorp performs. This license is, in essence, a licensor's covenant not to sue the licensee. *Hilgraeve Corp.* v. *Symantec Corp.*, 265 F.3d 1336, 1346 (Fed. Cir. 2001) (citation omitted). In turn, this court has held that a covenant not to sue deprives a court of declaratory judgment jurisdiction. *Amana Refrigeration, Inc.* v. *Quadlux, Inc.*, 172 F.3d 852, 855 (Fed. Cir. 1999) (citing *Super Sack Mfg. Corp.* v. *Chase Packaging Corp.*, 57 F.3d 1054, 1060 (Fed. Cir. 1995)). Accordingly, a licensor who has implicitly covenanted not to sue a licensee by virtue of the license agreement itself cannot seek a declaratory judgment of infringement. Moreover, in light of LabCorp's continuing royalty payments on the panel test, LabCorp cannot itself challenge the validity of a claim for which it

continues to pay royalties. *Cf. Gen-Probe Inc.*, 359 F.3d at 1382 (holding that a licensee who continued paying royalties to the licensor did not have sufficient apprehension of suit giving rise to declaratory judgment subject matter jurisdiction). The district court's opinion concerning the panel test's infringement of claim 18 was merely advisory. Accordingly, the district court lacked subject matter jurisdiction, and this court vacates that portion of the district court's judgment.

Breach of contract

The interpretation of a contract is a matter of state law. *Power Lift, Inc.* v. *Weatherford Nipple-Up Sys., Inc.*, 871 F.2d 1082, 1085 (Fed. Cir. 1989). A license agreement is at its core a contract. In this case, both parties agree that New Jersey law governs their rights and obligations under the license, including the termination clause. Under New Jersey law, breach of contract is a question of fact properly reserved for a jury. *Magnet Res., Inc.* v. *Summit MRI, Inc.*, 723 A.2d 976, 982 (N.J. Super. Ct. App. 1998). Thus, the standard of review for this court is whether substantial evidence supports the jury's finding.

The jury found that "LabCorp breached the license agreement by terminating it" for the Abbott test. LabCorp contends that it did not formally terminate the contract, because the contract requires that the licensee provide written notice. The record contains no evidence of a written termination. The record does show, however, that LabCorp stopped paying royalties on the total homocysteine tests. Refusal to pay royalties is a material breach of the license. *See Dow Chem. Co.* v. *United States*, 226 F.3d 1334, 1346 (Fed. Cir. 2000). A material breach, in turn, constitutes termination even where the license agreement termination clause does not expressly so provide. *See Apex Pool Equip. Corp.* v. *Lee*, 419 F.2d 556, 562 (2d Cir. 1969) (holding that a licensee's material breach implicitly gives rise to a licensor's right to terminate); *see also Ross-Simons of Warwick, Inc.* v. *Baccarat, Inc.*, 217 F.3d 8, 10 (1st Cir.

2000) ("Every contract involves a bargained-for exchange of obligations, the material breach of which by one party gives the other party a right to terminate."); Restatement (Second) of Contracts § 237 (1981). This court, therefore, affirms the jury's finding that LabCorp breached the license agreement.

Enhanced damages

LabCorp does not directly challenge the jury's willfulness finding. Instead, LabCorp contends that the district court did not discuss the *Read* factors for enhanced damages. *See Read Corp.* v. *Portec, Inc.*, 970 F.2d 816, 826-27 (Fed. Cir. 1992), *abrogated in part on other grounds*, *Markman*, 52 F.3d at 975. This court, therefore, addresses only the district court's grant of enhanced damages.

To be sure, this court has enunciated its strong preference that a district court set forth its rationale for an award of enhanced damages to facilitate appellate review. *Read*, 970 F.2d at 828 ("To enable appellate review, a district court is obligated to explain the basis for the award, particularly where the maximum amount is imposed."). On the other hand, this court has also recognized the competing public policy of conserving judicial resources and has cautioned that a remand is a "step not taken lightly." *Consol. Aluminum Corp.* v. *Foseco Int'l Ltd.*, 910 F.2d 804, 814 (Fed. Cir. 1990) (holding that a remand "should be limited to cases in which further action must be taken by the district court or in which the appellate court has no way open to it to affirm or reverse the district court's action under review"). As this court found in *Consolidated Aluminum*, "an appellate court need not close its eyes to the record where, as in this case, there is a way clearly open to affirm the district court's action." *Id.* at 814. Accordingly, this court considers the findings in the record for an abuse of discretion in doubling the infringement damages.

First, this court considers the second *Read* factor, namely whether LabCorp conducted an investigation regarding the scope of the '658 patent in order to form a good-faith belief.

Read Corp., 970 F.2d at 827. LabCorp concedes that Dr. Wentz alone determined that the Abbott total homocysteine tests did not infringe the '658 patent and therefore LabCorp would not need to continue paying royalties to Metabolite. Dr. Wentz himself testified during trial that his determination that the '658 patent did not extend to the Abbott total homocysteine tests was based solely on his interpretation of the license agreement between LabCorp and Metabolite. Moreover, Dr. Wentz testified that he did not consult the '658 patent itself. He also conceded his lack of training in patent law. Based on this evidence alone, the district court could easily have determined that LabCorp did not conduct a reasonable investigation into potential infringement by the Abbott total homocysteine tests. *See Underwater Devices Inc.* v. *Morrison-Knudsen Co., Inc.*, 717 F.2d 1380, 1390 (Fed. Cir. 1983) (affirming district court's grant of enhanced damages where defendant obtained incompetent opinion from in-house counsel who was not a patent attorney, did not consult the patent file histories, and prepared a memo containing "only bald, conclusory and unsupported remarks regarding validity and infringement of the [] patents").

LabCorp's failure to conduct a reasonable and independent investigation regarding the Abbott total homocysteine test is further highlighted by the very terms of the license agreement between LabCorp and Abbott Labs. In the license agreement, Abbott Labs specifically excludes the '658 patent from a warranty covered by an indemnity provision. The warranty specifically excludes:

> [A]ny claim of infringement which may arise under the subject matter of U.S. Patent 4,940,658 and any U.S. or foreign patents claiming priority therefrom or otherwise related thereto. *Except with respect to the foregoing* and at the time of signing this Agreement, Abbott has no reasonable knowledge of any infringement of third party patent rights that would arise from the use of the Imx Homocysteine Research Assay.

(emphasis added). By accepting this provision, LabCorp knew or should have known that Abbott Labs believed the use of the Abbott test might infringe the '658 patent. This language in the license agreement would have put a reasonable licensee on notice to conduct its own investigation regarding the '658 patent coverage of the Abbott total homocysteine test.

In addition to the second *Read* factor, the record also reflects that LabCorp is a large company with extensive financial means, i.e., *Read* factor four. LabCorp's infringing activities of claim 13 began in 1998 without any attempts to remedy the infringement, *Read* factors six and seven, respectively. The district court therefore had evidence before it warranting consideration of at least four *Read* factors.

That the district court did not explicitly set forth its rationale for awarding Metabolite enhanced damages based on LabCorp's willful indirect infringement is not fatal to its decision. As in *Consolidated Aluminum*, "[n]o useful purpose would be served by a remand to enable the district court to tell [this court] in express terms what [it] already know[s] from the record." 910 F.2d at 815. On the basis of the appellate record, this court can readily discern at least four *Read* factors that the district court likely considered when using its discretion to double the infringement damages. Accordingly, this court holds that the district court did not abuse its discretion in enhancing the infringement damages. The district court's failure to discuss the *Read* factors, although contrary to this court's strong preference for the enumerated bases underlying its decision, in this case was at most harmless error.

Injunction

The district court granted Metabolite's motion "to enjoin LabCorp from performing 'any homocysteine-only test, including without limitation homocysteine-only tests via the Abbott method.'"

LabCorp argues that the injunction is too broad because it extends beyond the scope of the claims. To the contrary, the injunction simply addresses LabCorp's specific acts constituting indirect infringement. LabCorp performs the assays upon request from physicians and in doing so indirectly infringes. The district court correctly enjoined LabCorp from infringement. LabCorp also argues that the injunction is defective in form under the Federal Rules of Civil Procedure, because Rule 65(d) requires that a district court "set forth the reasons" for issuing an injunction. The district court's order states that it "finds no sound reason for denying the injunction." While this statement does not explicitly set forth detailed reasons, the district court properly granted the injunction because LabCorp was found to infringe. *See W.L. Gore & Assocs., Inc.* v. *Garlock, Inc.*, 842 F.2d 1275, 1281 (Fed. Cir. 1988) ("[A]n injunction should issue once infringement has been established unless there is a sufficient reason for denying it."). The district court's brevity is not reversible error.

CONCLUSION

The district court did not err in denying JMOL, awarding enhanced damages, and granting the permanent injunction.

COSTS

Each party shall bear its own costs.

AFFIRMED

United States Court of Appeals for the Federal Circuit

03-1120

METABOLITE LABORATORIES, INC.
and COMPETITIVE TECHNOLOGIES, INC.,

Plaintiffs-Appellees,

v.

LABORATORY CORPORATION OF AMERICA HOLDINGS
(doing business as LabCorp),

Defendant-Appellant.

SCHALL, *Circuit Judge*, concurring-in-part, dissenting-in-part.

I agree with the majority's conclusions with respect to validity, the absence of a case or controversy regarding infringement of claim 18, breach of contract, enhanced damages, and the district court's injunction. However, I respectfully dissent from the majority's construction of claim 13 of the '658 patent. Because I think claim 13 covers only the correlation of elevated levels of homocysteine, I would remand the case for a recalculation of the damages resulting from indirect infringement.

Claim 13 of the '658 patent is an independent claim for a two-step method:

> 13. A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> assaying a body fluid for an elevated level of total homocysteine; and

> correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

Col. 41, ll. 58-65. Proper construction of the terms "correlating" and "elevated" is dispositive of the issue of infringement of claim 13. The district court construed "elevated" to mean "raised above the normal range," and "correlating" as "to establish a mutual or reciprocal relationship between." *Metabolite Labs., Inc.* v. *Lab. Corp. of Am. Holdings*, No. 99-Z-870, slip op. at 2-3 (D. Colo. Nov. 29, 2000) (*Markman Order*). Disagreeing with neither of these constructions, the majority holds that when a patient's homocysteine level is not "elevated," claim 13 may nevertheless be infringed because "correlating" includes establishing both a mutual relationship and a reciprocal relationship. The majority states:

> In essence, "correlating" means to relate the presence of an elevated total homocysteine level to either a cobalamin or folate deficiency, or both (i.e., a mutual relationship), and also to relate the absence of an elevated total homocysteine level to a deficiency in neither (i.e., a reciprocal relationship) . . . . [T]he specification and prosecution history confirm that the claim language "correlating," in the understanding of one of ordinary skill in this art field at the time of invention, includes both a mutual relationship between the presence of an elevated level of homocysteine and a vitamin deficiency and a reciprocal relationship between the absence of an elevated level of homocysteine and no vitamin deficiency.

In my view, the majority impermissibly expands the scope of claim 13 beyond the actual words of the claim.

I begin with what I see as the controlling principles of claim construction. When interpreting the claims of a patent, the court should look first to the intrinsic evidence of record: the claim, the specification, and, if in evidence, the prosecution history. *Vitronics Corp.* v. *Conceptronic, Inc.*,

90 F.3d 1576, 1582 (Fed. Cir. 1996). There exists within the intrinsic evidence a "hierarchy of analytical tools." *Digital Biometrics, Inc.* v. *Identix, Inc.*, 149 F.3d 1335, 1344 (Fed. Cir. 1998). First, the language of the claim should be considered—"[t]he actual words of the claim are the controlling focus." *Id.* The claim language defines the bounds of claim scope. *Bell Communications Research, Inc.* v. *Vitalink Communications Corp.*, 55 F.3d 615, 619-20 (Fed. Cir. 1995). Because the claims define the patentee's right to exclude others, "the claim construction inquiry, therefore, begins and ends in all cases with the actual words of the claim." *Renishaw plc* v. *Marposs Societa' per Azioni*, 158 F.3d 1243, 1248 (Fed. Cir. 1998).

If the meaning of a claim term is clear on its face, consideration of the remaining intrinsic evidence is restricted to determining if a deviation from the clear language of the claim is specified. *Interactive Gift Express, Inc.* v. *Compuserve Inc.*, 256 F.3d 1323, 1331 (Fed. Cir. 2001). The court may consider the patent specification in construing whether the patentee has intended for the meaning of a claim term to deviate from its ordinary meaning. *Vitronics*, 90 F.3d at 1582. The court may also consider the prosecution history, if it is in the record, for evidence of an intentional deviation from the plain meaning of a claim term. *Id.*

Beginning with the ordinary meaning of the claim terms, I too do not disagree with the district court's construction of the terms "elevated" and "correlating." Nor do I disagree with the majority's conclusion that the claim language does not require a further association between the level of total homocysteine and either a hematologic or neuropsychiatric abnormality or both. I cannot agree with the majority, however, that claim 13 is infringed when the test demonstrates that a patient's homocysteine level is *not* "elevated." The plain language of the claim requires "elevated" levels of homocysteine, and a heavy presumption weighs in favor of the ordinary and customary meaning of

that term. *CCS Fitness* v. *Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002). As the district court properly construed the term, "elevated" requires a level of homocysteine that is "raised above the normal range." *Markman Order*, slip op. at 2-3. Thus, for claim 13 to be infringed, the homocysteine assay must evince a level of homocysteine that is raised above the normal range. In short, in my view the majority disregards the explicit limitation in claim 13 that only an "elevated" level of homocysteine can be "correlated" with a vitamin deficiency.

There is no language in claim 13 addressing unelevated levels of homocysteine, nor language that unelevated levels of homocysteine are to be correlated with the absence of a vitamin deficiency. Ordinary meaning thus dictates that a patient's homocysteine level be "elevated" in order for a physician to practice claim 13. If the patient's homocysteine levels are not "elevated," by the plain language of the claim, there is no "correlating" to be done. The language of claim 13 does not suggest that the claim encompasses the correlation of unelevated levels with the absence of a deficiency, for the introductory phrase claims "a method for detecting a deficiency," without addressing at all the detection of the absence of a deficiency. '658 patent, col. 41, ll. 58-59.

We have repeatedly stated that "[c]ourts can neither broaden nor narrow claims to give the patentee something different than what he has set forth." *Tex. Instruments Inc.* v. *Int'l Trade Comm'n*, 988 F.2d 1165, 1171 (Fed. Cir. 1993) (quoting *Autogiro Co.* v. *United States*, 384 F.2d 391, 396 (Ct. Cl. 1967)); *Oak Tech., Inc.* v. *Int'l Trade Comm'n*, 248 F.3d 1316, 1329 (Fed. Cir. 2001). In this case, however, the majority has permitted claim 13 to be infringed even when homocysteine assays result in unelevated levels. The majority thereby broadens claim 13 to also include, although it is not expressly claimed, correlating unelevated levels of homocysteine with the absence of a vitamin deficiency.

Relying on language from the specification and the prosecution history, the majority brings assays that demonstrate unelevated levels of homocysteine within the province of claim 13 by focusing its construction on the term "correlating." The problem I have with this approach is that it ignores the term "elevated." In addition, because the term "elevated" in claim 13 is unambiguous on its face, the specification and prosecution history of the '658 patent may be consulted only to determine if the patentee intended to deviate from ordinary meaning. *Interactive Gift Express*, 256 F.3d at 1331. There is no evidence before us that any deviation was intended. Throughout the specification, the term "elevated" is consistently used to refer to levels that are raised above average. For example, the specification explains that

> The normal range for homocysteine in human serum is from about 7 to about 22 μmol/liter. *Homocysteine levels above these ranges* are indicative of cobalamin and/or folate deficiency . . . .
>
> * * * *
>
> When homocysteine levels are *elevated* in individuals without inherited defects, at least one of folate or cobalamin is deficient.

'658 patent, col. 9, ll. 23-29, 38-40 (emphases added). Nor is there any evidence from the prosecution history that the patentee relinquished this claim construction in an amendment or in an argument to overcome or distinguish a prior art reference. *Vitronics*, 90 F.3d at 1582. Accordingly, I construe Claim 13 to require an assay that demonstrates an "elevated" homocysteine level, or one "raised above the normal range," in order for the claim to be practiced.

Pursuant to this claim construction, claim 13 is only infringed when the assays performed by LabCorp reveal elevated levels of homocysteine. As LabCorp explains, and as Metabolite does not dispute, approximately eighty to eighty-four percent of the assays LabCorp processes reveal

unelevated levels of homocysteine. I would therefore vacate the jury's verdict that the assays resulting in unelevated levels of homocysteine infringed claim 13, and further vacate and remand the jury's verdict on damages for recalculation based only on those infringing assays that demonstrate elevated levels of homocysteine.

APPENDIX B

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLORADO
Senior Judge Zita L. Weinshienk

Civil Action No. 99-Z-870

METABOLITE LABORATORIES, INC.,
a Colorado corporation,
and
COMPETITIVE TECHNOLOGIES, INC.,
a Delaware corporation,
Plaintiffs-Appellees,

v.

LABORATORY CORPORATION OF AMERICA HOLDINGS
(doing business as LABCORP),
a Delaware Corporation,
Defendant-Appellant.

ORDER

This suit for patent infringement and breach of contract came before the Court for an eleven-day trial to a jury from November 5 to 20, 2001. The jury awarded Plaintiff Metabolite Laboratories, Inc. (Metabolite) $3,652,724.61 for breach of contract. The jury awarded Plaintiff Competitive Technologies, Inc. (CTI) $1,019,365.01 after finding that Defendant Laboratory Corporation of America (LabCorp) induced patent infringement and contributed to patent infringement. The parties have timely filed eleven post-trial motions.

First, Defendant moves for judgment as a matter of law, or alternatively for a new trial. The Court, however, determines

that there was substantial evidence supporting the jury's verdict, and will not reconsider LabCorp's arguments. Similarly, LabCorp's Motion To Take Judicial Notice will be denied. Defendant also filed a Motion To Alter Or Amend Judgment, to reflect LabCorp's affirmative defense and counterclaim of patent misuse. The issue was reserved by the Court at the time of trial. The Court, however, finds no basis for patent misuse.

Additionally, Plaintiffs have moved for enhanced damages and attorney fees for willful infringement. Upon a finding of infringement, where warranted, a court may increase the damages in an amount up to three times that found or assessed.[1] The jury in this case found that LabCorp willfully infringed claim 13 of the '658 patent. Upon a jury's finding of willfulness, this court must award enhanced damages or provide reasons for not doing so.[2] "The paramount determination in deciding to grant enhancement and the amount thereof is the egregiousness of the defendant's conduct based on all the facts and circumstances."[3]

In determining whether enhanced damages are appropriate, the Court may consider at least nine factors, enumerated in

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1 35 U.S.C. § 284.

2 *See Tate Access Floors, Inc. v. Maxcess Technologies, Inc.*, 222 F.3d 958 (Fed. Cir. 2000) ("While 'a finding of willful infringement does not mandate that damages be increased or that attorneys fees be awarded,' (citation omitted), after an express finding of willful infringement, 'a trial court should provide reasons for not increasing a damages award or for not finding a case exceptional for the purpose of awarding attorneys fees (citation omitted).").

3 *Read Corp. v. Portec. Inc.*, 970 F.2d 816, 826 (Fed. Cir. 1992), *abrogated in part on other grounds by Markman v. Westview Insts., Inc.*, 52 F.3d 967 (Fed. Cir. 1995).

Read Corp. v. *Portec, Inc.*[4] This Court has considered the *Read* factors carefully and concludes that enhanced damages doubling the jury verdict are appropriate, such that plaintiff CTI will be awarded an additional $1,019,365.01.

The Court may also award attorney fees for willful infringement "in exceptional circumstances."[5] A finding of willfulness "may be a sufficient basis in a particular case for finding the case 'exceptional' for purposes of awarding attorney fees to the prevailing patent owner."[6]

Plaintiff CTI bears the burden of "establishing entitlement to the award and documenting the appropriate hours expended and hourly rates."[7] Plaintiff has stated that the amount to be awarded will be established by affidavit submitted by counsel. The Court will consider Plaintiffs' request for attorney fees when it submits an affidavit.

Plaintiffs also move for a preliminary injunction pursuant to the Patent Act, 35 U.S.C. § 283. Plaintiffs seek to enjoin LabCorp from performing "any homocysteine-only test,

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4 *Id.* at 827. These nine factors are: (1) whether the infringer deliberately copied the ideas or design of another; (2) whether the infringer, when he knew of the other's patent protection, investigated the scope of the patent and formed a good-faith belief that it was invalid or that it was not infringed; (3) the infringer's behavior as a party to the litigation; (4) defendant's size and financial condition; (5) closeness of the case; (6) duration of defendant's misconduct; (7) remedial action by the defendant; (8) the defendant's motivation for harm; (9) whether the defendant attempted to conceal its misconduct.

5 35 U.S. § 285.

6 *Avia Group Intern., Inc.* v. *L.A. Gear California, Inc.*, 853 F.2d 1557, 1567 (Fed. Cir. 1988) (citations omitted).

7 *See Mares* v. *Credit Bureau of Raton*, 801 F.2d 1197, 1201 (10th Cir. 1986) (quoting *Hensley* v. *Eckerhart*, 461 U.S. 424 (1983)).

including without limitation homocysteine-only tests via the Abbott method." "It is the general rule that an injunction will issue when infringement has been adjudged, absent a sound reason for denying it."[8] This Court finds no sound reason for denying the injunction.

Finally, Plaintiffs move for prejudgment interest. An award of prejudgment interest is appropriate in patent infringement actions "absent some justification for withholding such an award."[9] "The purpose of prejudgment interest is solely to compensate the patentee for the loss of the use of royalty income the patentee would have been paid."[10] The rate awarded on the interest is within the discretion of the Court.[11]

The Court will award prejudgment interest to Plaintiff Metabolite based on an interest rate of 8% compounded annually, pursuant to Colo. Rev. Stat. § 5-12-102. The Court will not allow LabCorp, which breached the License Agreement, the benefit of the agreement's 60-day grace period in calculating the date each payment was due. Therefore, Metabolite's request for $473,946.97 will be granted.

As for Plaintiff CTI, the rate of prejudgment interest for patent infringement actions is not provided for in the Patent Act.[12] The Court determines that the 8% interest rate

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8 *Richardson* v. *Suzuki Motor Co., Ltd.*, 868 F.2d 1226, 1247 (Fed. Cir. 1989) (citation omitted).

9 *General Motors Corp.* v. *Devex*, 461 U.S. 648 (1983).

10 *Micro Chemical Inc.*, v. *Lextron, Inc.*, 161 F.Supp.2d 1187, 1210 (D. Colo. 2001) (citing *General Motors Corp.*, 461 U.S. at 654 (1983).

11 *Uniroyal Inc.*, v. *Rudkin-Wiley Corp.*, 939 F.2d 1540, 1545 (Fed. Cir. 1991).

12 *See* 35 U.S.C. § 284.

provided under Colo. Rev. Stat. § 5-12-102 is appropriate for CTI's award as well. CTI will be awarded $132,264.27. Therefore, it is

ORDERED that Defendant's Motion To File Corrected Memorandum In Support Of Laboratory Corporation of America Holding's Renewed Motion For Judgment As A Matter Of Law is granted. It is

FURTHER ORDERED that the clerk shall file stamp the tendered memorandum. It is

FURTHER ORDERED that Defendant's Renewed Motion For Judgment As A Matter Of Law is denied. It is

FURTHER ORDERED that Defendant's Alternative Motion For A New Trial is denied. It is

FURTHER ORDERED that Defendant's Motion To Alter Or Amend Judgment is denied. It is

FURTHER ORDERED that Defendant's Motion To Take Judicial Notice In Support Of Renewed Motion For Judgment As A Matter Of Law And In Opposition To Plaintiffs' Motion For A Permanent Injunction And Rule 7.1 Certification is denied. It is

FURTHER ORDERED that Plaintiffs' Motion For Enhanced Damages And Attorney Fees For Willful Infringement is granted as to enhanced damages to Plaintiff CTI in the amount of $1,019,365.01 and will be considered as to attorney fees upon submission of an affidavit from counsel. It is

FURTHER ORDERED that Plaintiffs' Motion For Permanent Injunction is granted. It is

FURTHER ORDERED that Plaintiff Metabolite Laboratories, Inc.'s Motion To Confirm Prejudgment Interest is granted in the amount of $473,946.97. It is

FURTHER ORDERED that Plaintiff Competitive Technologies, Inc's Motion For Prejudgment Interest is granted in the amount of $132,264.27. It is

FURTHER ORDERED that Defendant's Motion For Stay Of Execution Pending Disposition Of Post-Trial Motions is denied as moot. It is

FURTHER ORDERED that the judgment will be amended to reflect the additional amounts above.

DATED at Denver, Colorado, this 19 day of November, 2002.

BY THE COURT:

/s/
ZITA L. WEINSHIENK,
Senior Judge
United States District Court

APPENDIX C

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

No. 03-1120
DCT-99-Z-870

METABOLITE LABORATORIES, INC.
AND COMPETITIVE TECHNOLOGIES, INC.,
Plaintiffs-Appellees,

v.

LABORATORY CORPORATION OF AMERICA HOLDINGS
(doing business as LABCORP),
Defendant-Appellant.

ORDER

Filed on August 5, 2004

A combined petition for panel rehearing and for rehearing en banc having been filed by the APPELLANT, and a response thereto having been invited by the court and filed by the APPELLEE, and the petition for rehearing having been referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc and response having been referred to the circuit judges who are in regular active service,

UPON CONSIDERATION THEREOF, it is

ORDERED that the petition for panel rehearing be, and the same hereby is, DENIED and it is further

ORDERED that the petition for rehearing en banc be, and the same hereby is, DENIED.

The mandate of the court will issue on August 12, 2004.

For the court,

/s/ Jan Horbaly
Clerk

APPENDIX D

PERTINENT STATUTORY PROVISIONS

35 U.S.C. § 112 provides in pertinent part:

§ 112. Specification

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

* * * *

35 U.S.C. § 271 provides in pertinent part:

§ 271. Infringement of patent

(b) Whoever actively induces infringement of a patent shall be liable as an infringer.

Supreme Court, U.S.
FILED
DEC 3 - 2004
OFFICE OF THE CLERK

(3)

No. 04-607

IN THE

Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS (D/B/A LABCORP),

Petitioner,

v.

METABOLITE LABORATORIES, INC., AND COMPETITIVE TECHNOLOGIES, INC.,

Respondents.

On Petition For A Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

BRIEF FOR RESPONDENTS IN OPPOSITION

MARK A. PERRY
GIBSON, DUNN & CRUTCHER LLP
1050 Connecticut Avenue N.W.
Washington, D.C. 20036
(202) 955-8500

GLENN K. BEATON
Counsel of Record
J. GREGORY WHITEHAIR
GIBSON, DUNN & CRUTCHER LLP
1801 California Street
Denver, Colorado 80202
(303) 298-5700

Counsel for Respondents

QUESTION PRESENTED

Whether both lower courts correctly sustained the jury's factual finding that petitioner willfully induced infringement of respondents' patent.

RULE 29.6 STATEMENT

Respondents in this case are Competitive Technologies, Inc. and Metabolite Laboratories, Inc. Neither has any parent corporations. No publicly held company owns ten percent or more of the stock of either respondent.

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BRIEF FOR RESPONDENTS IN OPPOSITION

Respondents Metabolite Laboratories, Inc. and Competitive Technologies, Inc. respectfully submit that the petition for a writ of certiorari should be denied.

STATEMENT

After a jury trial, petitioner LabCorp was held liable for willfully inducing infringement of United States Patent No. 4,940,658, and ordered to pay damages to respondents. The Federal Circuit affirmed.

1. The '658 patent claims methods for detecting deficiencies in the human body of cobalamin (vitamin B_{12}) and folate (folic acid), which may cause serious illnesses if not treated. Pet. App. 2a. The inventors discovered that elevated levels of the amino acid homocysteine could serve as a marker for a deficiency in either cobalamin or folate. *Ibid.* Claim 13 of the '658 patent recites:

> A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> assaying a body fluid for an elevated level of total homocysteine; and
>
> correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

Id. at 3a (quoting '658 patent, col. 11, ll. 58-65).

Respondents licensed petitioner (and many others) to perform total homocysteine assays for the purpose of detecting cobalamin or folate deficiencies. Pet. App. 3a. "But in 1998, LabCorp switched to a total homocysteine assay developed by Abbott Laboratories . . . and discontinued

royalty payments to Metabolite for total homocysteine assays." *Ibid.*

Respondents sued petitioner for infringing the '658 patent. Pet. App. 3a. The jury found the patent to be valid, found petitioner liable for willfully infringing it, and assessed damages. *Id.* at 4a. The district court sustained the jury's findings (*ibid.*), and the court of appeals affirmed.

2. The court of appeals first construed the claim term "correlating." Pet. App. 7a. The court noted that petitioner had "urged the district court to construe 'correlate' according to its dictionary definition as a verb meaning 'to establish a mutual or reciprocal relation of' an elevated level of homocysteine," and that the district court adopted this construction. *Id.* at 8a. The court of appeals concluded that the claim language, the specification, and the prosecution history all supported this construction: "In sum, the specification and prosecution history confirm that the claim language 'correlating,' in the understanding of one of ordinary skill in this art field at the time of invention, includes both a mutual relationship between the presence of an elevated level of homocysteine and a vitamin deficiency and a reciprocal relationship between the absence of an elevated level of homocysteine and no vitamin deficiency." *Id.* at 12a. The court refused to allow petitioner, on appeal, "to change its claim construction position to read out the reciprocal relationship that it initially urged."

The court of appeals next concluded that substantial evidence supported the jury's verdict that petitioner willfully induced infringement of the '658 patent. The court noted that the inducement statute (35 U.S.C. § 271(b)) "requires proof of intent to induce infringement," and held that "[t]he record contains such evidence of intent." Pet. App. 14a-15a. Petitioner's "own publications ... promote total homocysteine assays for detecting cobalamin/folate deficiency" and "state that elevated total homocysteine

correlates to cobalamin/folate deficiency." *Id.* at 15a. "Because '[i]ntent is a factual determination particularly within the province of the trier of fact,'" the court declined to reverse the jury's verdict on induced infringement. *Ibid.* (citation omitted).

Finally, the court of appeals rejected petitioner's challenges to the validity of the '658 patent. The court concluded that claim 13 is not indefinite because "the claim construction exercise at the trial court produced a discernible and clear meaning" of the "correlating" step. Pet. App. 16a. The court concluded that the written description requirement was met because both the patent examiner and petitioner's "own expert and employees understood the meaning of 'correlating.'" *Id.* at 17a. And the court held that "[t]he specification also shows that the patentee enabled the claimed invention." *Ibid.*

ARGUMENT

The decision below is correct and does not conflict with any decision of this Court, the Federal Circuit, or any other court of appeals. Further review is therefore not warranted.

1. Petitioner's principal argument is that the Court should grant review to resolve an asserted "conflict" within the Federal Circuit's decisions regarding the intent element of induced infringement. Pet. 12. To the extent it exists at all, this "conflict" is not implicated on the facts of this case.

Petitioner contends that "[a] principal controversy underlying this case stems from two inconsistent Federal Circuit opinions issued over a decade ago ...." Pet. 12 (citing *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544 (Fed. Cir. 1990), and *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464 (Fed. Cir. 1990)). It is far from clear that these two authorities are, in fact, in conflict. *Hewlett-Packard* deals with ordinary infringement by inducement, while *Manville* deals with the special

circumstance of a corporate officer being held liable for infringement by inducement for directing the infringing acts of the corporation. Even in the narrow, and inapplicable, *Manville* scenario, at least one of the commentators cited by petitioner admits himself that the conflict may be largely in the minds of commentators. *See* Michael N. Rader, Toward a Coherent Law of Inducement to Infringe: Why the Federal Circuit Should Adopt the Hewlett-Packard Standard for Intent Under § 271(b), 10 Fed. Circuit B.J. 299, 324 (2000) ("Nonetheless, commentators have not given up on the *Manville Sales* formulation.").

In any event, there is no reason to believe that the Federal Circuit is incapable of resolving any conflict that may exist in its precedents on this point. *Wisniewski v. United States*, 353 U.S. 901, 902 (1957) ("It is primarily the task of a Court of Appeals to reconcile its internal difficulties").

Petitioner fails to inform the Court that this so-called "principal controversy" over infringement by inducement that forms the centerpiece of its certiorari request has never before been asserted in the protracted history of this litigation. To the contrary, petitioner cited *both* of the supposedly conflicting decisions in the court of appeals as articulating the *correct*, and apparently equivalent, standard for intentional inducement of patent infringement. LabCorp's Fed. Cir. Br., Opp. App. A, *infra* at 2a. ("[I]n any event, LabCorp cannot be liable for inducing infringement because CTI did not establish that LabCorp specifically intended that physicians use single homocysteine tests to determine deficiencies of cobalamin or folate." (citing both *Hewlett-Packard* and *Manville*) (emphasis in original)). The "conflict" on which petitioner relies therefore has not been properly preserved for this Court's review. *See, e.g., Taylor v. Freeland & Kronz*, 503 U.S. 638, 646 (1992) ("ordinarily, this Court does not decide questions not raised or resolved in

the lower court[s]") (quoting *Youakim v. Miller*, 425 U.S. 231, 234 (1976) (per curiam)); *United States v. Lovasco*, 431 U.S. 783, 788 n.7 (1977).

More importantly, resolving the "conflict" asserted by petitioner would have no impact on the jury's verdict. Petitioner contends that "under the *Manville Sales* analysis, a party like LabCorp could only be liable for inducement to infringe if it *knew or should have known its acts were inducing actual infringement.*" Pet. 14 (emphasis added). The jury in this case was instructed on precisely this test:

> To show infringement of claim 13 by inducement, plaintiffs must prove by a preponderance of the evidence that someone has directly infringed claim 13. If there is no direct infringement of claim 13 by anyone, defendant has not induced infringement. If you find that someone has directly infringed claim 13, it is not necessary to show that defendant LabCorp itself has directly infringed, if plaintiffs prove by a preponderance of the evidence that LabCorp actively and knowingly aided and abetted that direct infringement. Plaintiffs-must show that LabCorp *knew or should have known that its actions would induce actual infringement.* LabCorp cannot be liable for inducing infringement if it had no reason to be aware of the existence of the patent.

Jury Instruction No. 21, Opp. App. B, *infra* at 4a. This jury instruction is drawn from the model instructions published by the American Intellectual Property Law Association,[1] but

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[1] *See* AIPLA Model Jury Instruction on Inducing Infringement, *available at* http://www.aipla.org/Content/ContentGroups/Publi-

with one critical difference. The jury instruction in this case *omits* the phrase, found in the AIPLA model jury instruction, "actually intended to cause the acts that constitute direct infringement and that LabCorp" just before the language emphasized in the quote above. The jury instructions actually used in this case thus contain the stringent *Manville* standard now urged by petitioner, and omit the arguably less stringent *Hewlett-Packard* standard.

The rule reflected in the jury instruction is thus the same as petitioner now urges this Court to adopt, and a reversal with remand would make no difference. Consequently, accepting the Petition would lead this Court impermissibly to render a mere advisory opinion. *See, e.g., Lewis v. Continental Bank Corp.*, 494 U.S. 472, 477-79 (1990) (federal courts lack jurisdiction to adjudicate claims where the complaining party lacks a "personal stake in the outcome" or a "specific live grievance").

Petitioner stipulated to the jury instruction quoted above, understandably because it sets forth the more stringent *Manville* formulation that it urges on this court. Petitioner never appealed that instruction to the court of appeals. Therefore, the legal rule embodied in the instruction is not reviewable in this Court. *City of Springfield v. Kibbe*, 480 U.S. 257, 258-59 (1987).

This case is a particularly poor candidate for retooling the intent element of inducement given that the jury found by clear and convincing evidence that LabCorp's infringement was willful. LabCorp did not appeal that factual

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cations1/Guide_to_Model_Patent_Jury_Instructions.htm#Claim Construction6.

determination. Pet. App. 24a.[2] Unless this Court is prepared to review a fact finding, upon which no appeal was taken, LabCorp's argument to this Court must reduce to the following: its infringement was willful but unintentional.

To the extent petitioner is contending that the evidence was insufficient to support the jury's finding of inducement, that factual issue was resolved against petitioner by both the court of appeals and the district court. Further review in this Court is thus unwarranted. *See, e.g., Graver Mfg. Co. v. Linde*, 336 U.S. 271, 275 (1945) ("A court of law, such as this Court is, rather than a court for correction of errors in fact finding, cannot undertake to review concurrent findings of fact by two courts below in the absence of a very obvious and exceptional showing of error.").

2. Petitioner next claims that the court of appeals improperly construed the "correlating" step to encompass a reciprocal as well as a mutual relationship between homocysteine levels and vitamin deficiencies.[3] Pet. 20-23. Petitioner's contention is that the "correlating" step should instead be construed to cover a positive result but not a negative result. In rejecting that attack, the Federal Circuit applied well-settled rules of claim construction, looking first to the ordinary meaning of the terms at issue and then to the specification and file history of the patent. The Federal Circuit also noted correctly that the record shows that petitioner itself proposed the very construction that it now disputes: That the "correlating" step refers to a "mutual" or a

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[2] LabCorp did appeal the district court's award of enhanced damages for the willful infringement. The court of appeals unanimously upheld that award. Pet. App. 27a & 28a.

[3] Even the lone dissenter in the court of appeals, while apparently disputing the jury's application of the claim construction, stated "I too do not disagree with the district court's construction of the terms 'elevated' and 'correlating.'" Pet. App. 30a.

"reciprocal" relationship, a proposal that the district court adopted and the Federal Circuit affirmed. The mutual relationship applies to one test outcome, and the reciprocal relationship applies to the other test outcome. The court of appeals observed "that the perfect symmetry between 'mutual or reciprocal' and 'presence or absence' shows that the district court correctly placed the term 'correlating' in its proper context with its proper meaning." Pet. App. 11a.

This patent-specific issue of claim construction was thoroughly vetted in both the district court and the court of appeals. The majority of the court of appeals agreed with the district court – and, indeed, with the construction that petitioner had previously advanced in the district court – that the construction urged by petitioner on appeal was unduly narrow and was not consistent with the claim language, the ~~specification, or~~ the prosecution history. This Court does not sit to review such case-specific determinations. *Cf. United States v. Johnson*, 268 U.S. 220, 227 (1925).

3. Petitioner also contends that the patent is invalid. Pet. 23-26. But petitioner's own witnesses and medical expert testified that they had no difficulty deciphering the meaning of the claim at issue. Nine of petitioner's competitors pay royalties on this patent with no difficulty in deciphering it. For six years, petitioner paid too, until a LabCorp technician with no training in patent law unilaterally decided to stop paying in an effort to cut costs. That was a (misguided) business decision, not evidence of invalidity.

Petitioner's validity argument, like the claim construction argument, does not extend beyond the specific patent at issue in this case. The court of appeals and the district court both rejected petitioner's invalidity arguments on the basis of the evidence submitted to the jury. There is no reason for this Court to revisit that fact-specific determination. *See Graver Mfg.*, 336 U.S. at 275 (declining

to reconsider fact-based validity determinations made by both lower courts).

4. Finally, petitioner predicts dire consequences for the future of the Nation's healthcare if the decision below stands. Pet. 2, 26-30. But petitioner's assertion that the Federal Circuit has effectively allowed a monopoly on a basic scientific fact and enjoined physicians from engaging in "thought processes" is mere hyperbole.[4] Not a single physician has been enjoined, sued or even threatened with suit, and none will be. The method patent at issue cannot be infringed by a physician's mere thought processes, because the patent requires a further distinct and physical step: the step of assaying for total homocysteine. Unlike the "author of a medical textbook" to whom petitioner compares itself (Pet. 18), petitioner performs that physical step and thereby completes the act of induced infringement. The jury concluded that petitioner is liable for violating the law in this regard. The district court agreed, the court of appeals panel agreed, and the court of appeals *en banc* unanimously denied the petition for rehearing. Nothing in that factbound determination implicates important legal issues of general applicability or warrants review by this Court.

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted.

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[4] Petitioner's warning of "nationwide confusion" over this case (Pet. 2) is similarly hysterical. As of the date of this Response, the case has not attracted a single article or commentary, and no amicus briefs were filed with the court of appeals or this Court.

MARK A. PERRY
GIBSON, DUNN & CRUTCHER LLP
1050 Connecticut Avenue N.W.
Washington, D.C. 20036
(202) 955-8500

GLENN K. BEATON
Counsel of Record
J. GREGORY WHITEHAIR
GIBSON, DUNN & CRUTCHER LLP
1801 California Street
Denver, Colorado 80202
(303) 298-5700

December 3, 2004.

APPENDIX

APPENDIX A

United States Court of Appeals for the Federal Circuit

03-1120

METABOLITE LABORATORIES, INC., and
COMPETITIVE TECHNOLOGIES, INC.,

Plaintiffs-Appellees,

- v.

LABORATORY CORPORATION OF AMERICA
HOLDINGS (doing business as LabCorp),

Defendant-Appellant.

Appeal from the United States District Court for the
District of Colorado in 99-Z-870,
District Judge Zita L. Weinshienk

CORRECTED BRIEF FOR APPELLANT LABORATORY CORPORATION OF AMERICA HOLDINGS

Of Counsel:

JOHN P. HIGGINS
ALSTON & BIRD, LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, North Carolina 28280
(704) 444-1000

JONATHAN S. FRANKLIN
CATHERINE E. STETSON
HOGAN & HARTSON L.L.P.
555 Thirteenth Street, N.W.
Washington, D.C. 20004-1109
(202) 637-5766

Counsel for Appellant Laboratory
Corporation of America Holdings

February 19, 2003
(Corrected Brief filed March 12, 2003)

* * * [34]

4. LabCorp Did Not Induce Infringement.

Without the necessary proof of direct infringement, CTI's claim of induced infringement fails. See supra at 25. But in any event, LabCorp cannot be liable for inducing infringement because CTI did not establish that LabCorp [*35] specifically intended that physicians use single homocysteine tests to determine deficiencies of cobalamin or folate. See Hewlett-Packard Co., 909 F.2d at 1469, 15 USPQ2d at 1529 ("proof of actual intent to cause the acts which constitute infringement is a necessary prerequisite to finding active inducement"); Manville Sales Corp. v. Paramount Sys., Inc., 917 F.2d 544, 553, 16 USPQ2d 1587, 1594 (Fed. Cir. 1990) (alleged active inducer "must be shown * * * to have knowingly induced infringement").

The trial evidence overwhelmingly demonstrated that LabCorp intended for single homocysteine tests to be used to screen for risk of heart disease, rather than to determine deficiencies of cobalamin or folate. As noted, Dr. Allen himself observed that it would not be good medical practice to use a single homocysteine test to determine vitamin deficiencies, A7950, and LabCorp's Director of Toxicology agreed. A7971.

LabCorp's own materials make the same point. The entry for the single homocysteine test in LabCorp's Directory of Services expressly refers physicians to the royalty-bearing panel test to determine deficiencies in folate. A8501, A8505. The Directory's entry for the panel test, in turn, does not refer physicians to the single homocysteine test. A8499. LabCorp's patient report for the single homocysteine test likewise refers physicians to the panel test to determine vitamin deficiencies, specifically cautioning that the single test "is [*36] intended to be used as an independent risk factor for vascular disease and is NOT for the diagnosis of folate or

cobalamin deficiency." A8446. LabCorp beyond doubt lacked specific intent to cause infringement.

* * *

[*63]

Respectfully submitted,

/s/
Jonathan S. Franklin
Catherine E. Stetson
HOGAN & HARTSON L.L.P.
555 Thirteenth Street, N.W.
Washington, D.C. 20004-1109
(202) 637-5766

Counsel for Appellant Laboratory Corporation of America Holdings

Of Counsel:

John P. Higgins
ALSTON & BIRD, LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, North Carolina 28280
(704) 444-1000

February 19, 2003
(Corrected Brief filed March 12, 2003)

APPENDIX B

JURY INSTRUCTION NO. 21

To show infringement of claim 13 by inducement, plaintiffs must prove by a preponderance of the evidence that someone has directly infringed claim 13. If there is no direct infringement of claim 13 by anyone, defendant has not induced infringement. If you find that someone has directly infringed claim 13, it is not necessary to show that defendant LabCorp itself has directly infringed, if plaintiffs prove by a preponderance of the evidence that LabCorp actively and knowingly aided and abetted that direct infringement. Plaintiffs must show that LabCorp knew or should have known that its actions would induce actual infringement. LabCorp cannot be liable for inducing infringement if it had no reason to be aware of the existence of the patent.

If you find that someone has directly infringed claim 13 and that LabCorp knew or should have known that its actions would induce direct infringement, you may find that LabCorp induced another to infringe claim 13 if it provided instructions and directions to perform the infringing act through labels, advertising or other sales methods. You may find that LabCorp induced infringement even if there is an express warning against the infringement, if the material containing the warning nonetheless invites the infringing activities under the circumstances. You may find that LabCorp induced infringement by supplying the components that are used in an infringing method or apparatus with the knowledge and intent that its customer would directly infringe by using the components to make, use or sell the patented invention.

(2)

No. 04-607

Supreme Court, U.S.
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IN THE

Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS (doing business as LabCorp),

Petitioner,

v.

METABOLITE LABORATORIES, INC. and COMPETITIVE TECHNOLOGIES, INC.,

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

REPLY BRIEF FOR PETITIONER

JOHN P. HIGGINS
ALSTON & BIRD, LLP
Bank of America Plaza
101 South Tryon Street
Suite 4000
Charlotte, NC 28280
(704) 444-1000

JONATHAN S. FRANKLIN*
CATHERINE E. STETSON
JESSICA L. ELLSWORTH
HOGAN & HARTSON L.L.P.
555 Thirteenth Street, N.W.
Washington, D.C. 20004
(202) 637-5766

* Counsel of Record

Counsel for Petitioner

WILSON-EPES PRINTING CO., INC. – (202) 789-0096 – WASHINGTON, D. C. 20001

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STATUTE:

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REPLY BRIEF FOR PETITIONER

Respondents' opposition is most notable for what it concedes. Respondents do not dispute that the Federal Circuit construed a patent to confer a legally-protected monopoly barring any doctor in the Nation from even *thinking* about a well-known scientific correlation when looking at a test result. They do not dispute that the Federal Circuit construed a patent claim to include both what is expressly claimed and the exact opposite of what is claimed. They do not dispute that the Federal Circuit failed to apply the induced infringement standard of *Manville Sales Corp.* v. *Paramount Sys., Inc.*, 917 F.2d 544 (Fed. Cir. 1990), in reviewing the evidence. And, as they must, respondents agree that the sum

total of the evidence that the court found sufficient to impose liability on LabCorp for induced infringement was publication of a basic scientific fact. Opp. 2-3.

Respondents accordingly fail to grapple with, much less explain away, the danger the medical community faces if this decision is permitted to stand unreviewed. The Federal Circuit has construed a patent to grant a monopoly over a scientific fact, holding that doctors directly infringe the patent by thinking about a basic medical fact critical for treatment decisions, and that a third party induces infringement merely by reminding doctors of this fact. This decision—if allowed to stand—poses a severe threat to patient care. The opposition fails to dispel the intolerable uncertainty the Federal Circuit has imposed on all those who seek to provide doctors with the medical facts necessary for effective treatment of their patients, and all those who seek to comply with what should be uniform legal standards under the Patent Act. The Court should grant certiorari to resolve this uncertainty.

1. Instead of arguing that the record contains sufficient evidence to impose liability under the proper standard for inducement to infringe, respondents resort to arguing that LabCorp has not preserved its argument on that standard. Opp. 4. That is not so. Whether LabCorp can be held liable for induced infringement under the correct legal standard has been a centrally-contested issue throughout this case. LabCorp argued consistently before the District Court and the Federal Circuit that it could not be liable for inducement because it did not knowingly intend doctors to infringe the '658 patent—the standard articulated by the Federal Circuit in *Manville Sales*. *See* LabCorp Fed. Cir. Br. 35-36.[1] In addition to explicitly referencing the *Manville Sales* standard, LabCorp consistently reinforced its argument that liability

[1] LabCorp stated consistently that it intended single homocysteine tests be used to screen for risk of heart disease, not to aid in a vitamin-deficiency diagnosis. *Id.* at 35.

was improper through citations to other cases in which *Manville Sales* was applied, including *Minnesota Mining & Manufacturing Co.* v. *Chemque, Inc.*, 303 F.3d 1294, 1305 (Fed. Cir. 2002), and *Warner-Lambert Co.* v. *Apotex Corp.*, 316 F.3d 1348, 1363 (Fed. Cir. 2003). *See* LabCorp Fed. Cir. Br. 27, LabCorp Fed. Cir. Reply Br. 16; *see also* LabCorp Pet. for Reh'g 1 (stating that the panel decision was contrary to *Warner-Lambert* and *Minnesota Mining*).[2]

Respondents do not contest that the Federal Circuit failed to apply the *Manville Sales* standard here. Instead they claim that the District Court's *jury instruction*, which hewed to the *Manville Sales* standard, was not appealed and is therefore not reviewable. Opp. 5-6. That is a classic red herring. LabCorp's petition is not premised on the trial court's jury instruction, because LabCorp *agrees* that the jury was properly instructed on this point. The petition seeks review of the *Federal Circuit*'s failure to adopt or apply *Manville Sales* in reviewing the sufficiency of the evidence. The Federal Circuit instead applied an alternate, lesser standard for induced infringement—the *Hewlett-Packard* standard—to uphold a finding of liability against LabCorp. And as explained in the petition, if the Federal Circuit had examined the evidence under the *Manville Sales* standard, it should have reversed the District Court's judgment because the sole evidence relied on by the Federal Circuit—LabCorp's dissemination of a basic medical fact—is indisputably insufficient to establish inducement liability under that stand-

[2] Respondents note that LabCorp cited both *Manville Sales* and *Hewlett-Packard Co.* v. *Bausch & Lomb Inc.*, 909 F.2d 1464 (Fed. Cir. 1990), in its Federal Circuit briefing. Opp. 4. Given that the Federal Circuit has announced two divergent standards, however, LabCorp was well-advised to have cited both. Indeed, as explained in the petition, this Court's intervention is needed precisely because the Federal Circuit has adopted two inconsistent standards, each of which purports to be controlling on parties before that court and those who seek to obey the patent laws.

ard. Pet. 16-19. *Nowhere* in the opposition do respondents explain how that evidence can satisfy *Manville Sales*.[3]

There can only be one standard for determining whether the intent requirement of inducement to infringe is satisfied. Yet the Federal Circuit has embraced two such tests over the years, fostering well-recognized and untenable confusion in the law.[4] Respondents nonetheless opine that the Federal Circuit should be capable of "resolving any conflict that may exist in its precedents." Opp. 4. But as LabCorp explained in the petition, this conflict has existed for nearly fifteen years, with no movement within that court to resolve it. And the Federal Circuit, of course, is unique among circuit courts because its patent precedents will not be tested or influenced by the decisions of any other federal court of appeals. The Federal Circuit has demonstrated its inability to resolve the conflict between the *Hewlett-Packard* and *Manville Sales*

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[3] As noted in the petition, LabCorp was held to have induced infringement of the '658 patent based on its publication of a medical fact, despite having never provided any guidance, instruction, direction, or encouragement to doctors on how to infringe the patent, and even though LabCorp *and* the patent "inventor" understood that doctors order a single homocysteine test to screen for risk of heart disease, not to aid in the diagnosis of vitamin deficiency. *See* Pet. 5-6.

[4] Respondents incorrectly argue that *Hewlett-Packard* "deals with ordinary infringement by inducement" and *Manville Sales* deals with a corporate officer inducing infringement. Opp. 3-4. Each case purports to establish the general standard for induced-infringement liability, and the Federal Circuit has applied *Manville Sales* in cases involving "ordinary infringement by inducement." *See, e.g., Minnesota Mining*, 303 F.3d at 1305; *Mentor H/S, Inc.* v. *Medical Device Alliance, Inc.*, 244 F.3d 1365, 1379 (Fed. Cir. 2001). Indeed, the Federal Circuit *itself* has acknowledged that *Hewlett-Packard* and *Manville Sales* state conflicting liability standards. *See Insituform Tech. Inc.* v. *CAT Contracting, Inc.*, 385 F.3d 1360, 1378 (Fed. Cir. 2004); Pet. 13.

standards, and this case squarely presents the situation where the outcome differs depending on the standard by which the evidence is judged.[5]

2. The Federal Circuit's ruling warrants review for an independent reason: the majority's decision—which held that the term "elevated" in Claim 13 also could be construed to include an opposite "unelevated" state—contravenes this Court's long-held recognition that the public must be able to rely on the express claims of a patent. *See General Elec. Co.* v. *Wabash Appliance Corp.*, 304 U.S. 364, 369 (1938); Pet. 20-22.

Respondents say nothing about the opinion's jarring claim-construction ruling other than to incorrectly assert that LabCorp has offered varying interpretations of the claim term "correlating." Opp. 7-8. LabCorp has consistently argued at each stage of this case that the word "correlating"—whatever it means—expressly applies only to "elevated" results. Claim 13 of the patent provides that when a test indicates an *elevated* level of homocysteine, it should be correlated with a vitamin deficiency. Although the patent provides no guidance as to what "correlating" means, it explicitly limits the circumstances under which one should "correlate" to those where there is an *elevated* level of homocysteine. The

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[5] Respondents incorrectly assert that LabCorp did not appeal the jury's willfulness determination. Opp. 6-7. LabCorp expressly raised that argument below. *See, e.g.*, LabCorp Fed. Cir. Br. 54 ("Because, for the reasons set forth above, the judgment of infringement cannot stand, the findings of willfulness and enhanced damages should also be reversed. Those findings should also be reversed and vacated for independent reasons."). LabCorp raised the same arguments against both the willfulness finding and the enhanced damages award, *id.* at 54-58, and the Federal Circuit considered all those arguments in the latter context. Pet. 24a. In any event, the principal challenges here are to the holdings on induced infringement and invalidity; if either of those holdings is reversed, the finding of willful infringement necessarily falls as well.

patent simply does not cover correlation of *unelevated* results. *See* Pet. App. 30a-33a (Schall, J., dissenting).

Respondents understandably fail to justify a construction of Claim 13 that includes within its scope both elevated *and* unelevated levels. Nor do they explain how physicians can practice the claim—that is, how physicians can "correlate"—where test results indicate an unelevated homocysteine level. On this point, and as the panel's dissenting judge observed, Claim 13 is simple and direct: without an elevated level, there is no correlating to be done.[6]

3. The opposition does not respond to LabCorp's argument that this patent, which merely teaches a scientific fact rather than describe an actual invention making use of that fact, is indefinite, insufficiently described, and non-enabling as a matter of law. A claim that simply directs a practitioner to "correlate" a test result with a medical condition—without any definition of what "correlate" means beyond the vague, judicially-created meaning "think about the basic scientific association between"—fails all the requirements of patent validity. *See* 35 U.S.C. § 112 ¶¶ 1, 2. It also fails this Court's long-held standard that a method patent cannot just state a scientific fact but must teach the public to *do something* specific with that fact. *See, e.g.*, *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948); Pet. 23-26. The invalidity argument is thus deeply intertwined with the other arguments presented in the petition and should be considered together with them.

4. Respondents fail to discount the general applicability of the Federal Circuit's decision or the consequences of allowing it to stand. Opp. 9. To the contrary, they do not deny that the Federal Circuit has upheld a patent purporting to cover a doctor's thought processes. Such a patent construction

[6] As respondents do not contest, the claim limitation at issue here was specifically added to overcome the prior art. Pet. 4, 20.

provides a legally-protected monopoly over a basic scientific fact in a way that prevents a doctor from using his or her medical knowledge without fear of infringement. Pet. 26-27. While respondents assert that they have not yet decided to sue doctors, Opp. 9, they stop short of asserting that the doctors are not infringing the patent. That is because, under respondents' theory and the Federal Circuit's holding, doctors commit direct infringement every time they order an unlicensed homocysteine test and merely *think* about the scientific connection between homocysteine level and vitamin deficiencies. It is immaterial that the patent also requires that a test be done. *Id.* For the patent specifies no particular testing method and the Federal Circuit held that the critical act of infringement occurs whenever a doctor "correlates" the result of a test in his or her mind by thinking that the result may (or may not) signify something about a vitamin deficiency.

Testing methods are patentable; medical facts are not. The sole basis on which respondents distinguish LabCorp from the author of a medical textbook—who would equally be liable for infringement of this patent under the Federal Circuit's ruling—is that LabCorp used to perform single homocysteine tests. This distinction is irrelevant to the Federal Circuit's legal analysis in this case. The court did not distinguish third parties that run tests from third parties that do not; it held LabCorp liable because it was a third party that published to doctors a medical fact that allegedly induced them to order unlicensed tests. If LabCorp is liable here for inducing doctors to infringe, then so too is anyone else who similarly informs doctors that a homocysteine test result might say something about vitamin levels.

For all these reasons, the Court should grant certiorari. But moreover, patent disputes—particularly those with broad national import like this one—are also especially appropriate for inviting the Solicitor General to express the United States' view, given that one panel of Federal Circuit judges can issue a decision governing every lower federal court in

the country. LabCorp accordingly suggests that the Court may wish to invite the Solicitor General to express the views of the United States in this case, as the Court recently has done in other cases presenting similar potential for national impact. Such an invitation is often properly extended when the case on petition involves patent law.[7]

CONCLUSION

For the foregoing reasons, and those in the petition, the petition for a writ of certiorari should be granted and the judgment below reversed.

Respectfully submitted,

JOHN P. HIGGINS
ALSTON & BIRD, LLP
Bank of America Plaza
101 South Tryon Street
Suite 4000
Charlotte, NC 28280
(704) 444-1000

JONATHAN S. FRANKLIN*
CATHERINE E. STETSON
JESSICA L. ELLSWORTH
HOGAN & HARTSON L.L.P.
555 Thirteenth Street, N.W.
Washington, D.C. 20004
(202) 637-5766

* Counsel of Record

Counsel for Petitioner

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[7] *See, e.g.*, *Honeywell Int'l, Inc.* v. *Hamilton Sundstrand Corp.*, 125 S. Ct. 458 (2004); *McFarling* v. *Monsanto Co.*, 125 S. Ct. 348 (2004); *Merck KGaA* v. *Integra Lifesciences I, Ltd.*, 125 S. Ct. 237 (2004); *Duke Univ.* v. *Madey*, 538 U.S. 959 (2003); *Monsanto Co.* v. *Bayer CropScience S.A.*, 537 U.S. 1027 (2002); *Micrel, Inc.* v. *Linear Tech. Corp.*, 537 U.S. 946 (2002).

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JOHN P. HIGGINS
ALSTON & BIRD, LLP
Bank of America Plaza
101 South Tryon Street
Suite 4000
Charlotte, NC 28280
(704) 444-1000

JONATHAN S. FRANKLIN*
CATHERINE E. STETSON
JESSICA L. ELLSWORTH
HOGAN & HARTSON L.L.P.
555 Thirteenth Street, N.W.
Washington, D.C. 20004
(202) 637-5766

* Counsel of Record

Counsel for Petitioner

WILSON-EPES PRINTING CO., INC. – (202) 789-0096 – WASHINGTON, D. C. 20001

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SUPPLEMENTAL BRIEF FOR PETITIONER

Pursuant to S. Ct. R. 15.8, petitioner LabCorp respectfully submits this supplemental brief to inform the Court of a new development that may bear upon this case. After the petition was filed in this case, the Court granted certiorari in *Metro-Goldwyn-Meyer Studios Inc.* v. *Grokster, Ltd.*, No. 04-480 ("*MGM*"). And just recently, opening briefs were filed in *MGM* making clear that the interpretation and application of the standard for induced infringement—a central issue in this petition—is also a central issue to be decided in *MGM*. Accordingly, although LabCorp continues to believe that its petition should be granted for all the reasons set forth in the petition and reply, the Court should at the very least hold the

petition pending a decision in *MGM* and then vacate the judgment and remand the case for further consideration in light of that decision.

1. A central question presented in this petition is the proper application of the standard for inducement to patent infringement—a question on which the Federal Circuit has been hopelessly divided for years. Like this case, *MGM* involves a claim of secondary infringement against a party that committed no direct infringement. The opening briefs in *MGM*, filed January 24, 2005, have now confirmed that the application of the standard for inducement to infringement—a standard asserted to be common to both the copyright infringement at issue in *MGM* and the patent infringement at issue in this case—is also a principal issue in *MGM*.

Indeed, the *MGM* petitioners' primary argument is that the Court should measure the conduct of the defendant there under the standards governing induced patent infringement, just as the Court relied on patent law to determine the standards for contributory copyright infringement in *Sony Corp. of Am.* v. *Universal City Studios, Inc.*, 464 U.S. 417 (1984). *See* Brief for Motion Picture Company and Recording Studio Petitioners at 23-29 ("*MGM* Petitioners' Br."). As the *MGM* petitioners argue, and as LabCorp specifically noted in its petition, the inducement standard is not unique to patent law. *See* LabCorp Pet. 14-15 (noting that the conflict "extends beyond patent law" to include general standards for aiding and abetting liability). Thus, the *MGM* petitioners specifically rely on Section 271(b) of the Patent Act—a principal subject of LabCorp's petition—and they cite *Hewlett-Packard Co.* v. *Bausch & Lomb Inc.*, 909 F.2d 1464 (Fed. Cir. 1990)—which was applied by the Federal Circuit in this case and is the fount of the lower court conflict identified in LabCorp's petition. *See MGM* Petitioners' Br. 28-29 & n.18; *compare* LabCorp Pet. 12-19.

Amici supporting the *MGM* petitioners—including the United States—as well as amici supporting neither side,

likewise rely heavily on what they assert to be the standard for inducement to patent infringement under Section 271(b). *See, e.g.*, U.S. Br. 27-30; American Intellectual Property Law Ass'n Br. 5, 13-24 ("AIPLA Br."); Br. for Utah, *et al.* at 17; IEEE-USA Br. 14-28; Prof. Lee A. Hollaar Br. 7-20; Br. for Law Professors, *et al.* at 8; Nat'l Academy of Recording Arts & Sciences Br. 10-11. Some specifically urge the Court to adopt the overly lenient *Hewlett-Packard* standard for induced infringement, which was applied by the Federal Circuit in this case and criticized in LabCorp's petition. *See* AIPLA Br. 5, 6, 7, 15, 16, 20, 21; Law Professors' Br. 8.

2. By citing the positions on induced infringement taken by the *MGM* petitioners (the plaintiffs in that case) and their supporting amici, LabCorp by no means endorses those positions. Indeed, although the *MGM* defendants and their amici have yet to file their briefs, it can reasonably be anticipated that they would have divergent views on the proper standard for induced infringement.

The important point is that the issues presented by the *MGM* petitioners make it likely that the Court's decision in that case will opine on the appropriate standard for induced infringement to be applied under both copyright and patent law. In that event, it would be appropriate for the Court to vacate the Federal Circuit's judgment in this case and remand for further consideration in light of *MGM*. *See, e.g.*, *Lawrence* v. *Chater*, 516 U.S. 163, 167-168 (1996) (GVR appropriate where "an intervening factor has arisen that has a legal bearing upon the decision") (citation omitted). And if *MGM* does not clarify the confusion that presently exists over the proper standard, then certiorari should be granted in this case for all the reasons set forth in the petition.

Indeed, certiorari can and should be granted in this case irrespective of *MGM*, given the intractable conflicts on the various questions presented, the nationwide importance of the case to medical treatment, and the deeply flawed holding below, which upheld a patent claiming a monopoly to

prevent doctors from even *thinking* about a well-known scientific correlation used in medical treatment, imposed multi-million dollar liability on a third party for merely informing the doctors of that basic scientific fact, and enjoined LabCorp from directly performing critical medical tests no matter the method used to perform them. Thus, although *MGM* may well impact this petition, the Federal Circuit's holding in this case should be reversed, or at a minimum vacated, regardless of the outcome of that case.

CONCLUSION

For the foregoing reasons, and those in the petition, the petition for a writ of certiorari should be granted and the judgment below reversed. But at a minimum, the Court should hold the petition pending a decision in *MGM*, and then vacate the judgment below and remand for further consideration in light of that decision.

Respectfully submitted,

JOHN P. HIGGINS
ALSTON & BIRD, LLP
Bank of America Plaza
101 South Tryon Street
Suite 4000
Charlotte, NC 28280
(704) 444-1000

JONATHAN S. FRANKLIN*
CATHERINE E. STETSON
JESSICA L. ELLSWORTH
HOGAN & HARTSON L.L.P.
555 Thirteenth Street, N.W.
Washington, D.C. 20004
(202) 637-5766

* Counsel of Record

Counsel for Petitioner

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JONATHAN S. FRANKLIN*
CATHERINE E. STETSON
JESSICA L. ELLSWORTH
HOGAN & HARTSON L.L.P.
555 Thirteenth Street, N.W.
Washington, D.C. 20004
(202) 637-5766

* Counsel of Record

Counsel for Petitioner

WILSON-EPES PRINTING CO., INC. – (202) 789-0096 – WASHINGTON, D. C. 20001

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SUPPLEMENTAL BRIEF FOR PETITIONER

Pursuant to S. Ct. R. 15.8, petitioner LabCorp responds to the brief filed by the Solicitor General at the Court's invitation. The Court asked for the views of the United States on a straightforward yes-or-no question. The Court expressly asked the Solicitor General to assume that the patent claimed only a two-step method—(1) "measure the level of the relevant amino acids using any device, whether the device is, or is not, patented" and (2) "notice whether the amino acid is elevated and, if so, conclude that a vitamin B deficiency exists." The Court then asked whether that patent claim, as so construed, is invalid "because one cannot patent 'laws of nature, natural phenomena, and abstract ideas.' " 125 S. Ct. 1413 (citing *Diamond* v. *Diehr*, 450 U.S. 175, 185 (1981)).

The Solicitor General's brief, however, does not answer the question. If it had, the answer would have to have been "yes." For the United States' *own* reasoning shows that the construction of the patent posited by the Court—which accurately conveys the Federal Circuit's basic holding—would render the patent invalid. According to the Federal Circuit, Claim 13 is infringed whenever a doctor looks at a homocysteine test result—*regardless* of how the test result was obtained—and *thinks in his or her mind* that it may signify a vitamin deficiency. As the United States' own brief (and common sense) demonstrate, such an attempt to monopolize a basic scientific correlation is impermissible. No further factual development is needed to reach that result. Moreover, that basic question is squarely presented by the decision below, was posed in the petition for certiorari and below, and is also a fundamental legal question that the Court can and should answer for itself. The petition should be granted.

I. THE UNITED STATES' OWN REASONING DEMONSTRATES THE PATENT'S INVALIDITY

The United States admits that "Claim 13 appears to *involve* * * * a [non-patentable] natural phenomenon, because it

asserts and relies on the existence of a naturally occurring correlation between elevated levels of total homocysteine and deficiencies in cobalamin or folate." U.S. Br. 6 (emphasis in original). But it then incorrectly suggests that further factual development "may" (*id.* at 5) be warranted to address the specific question posed by this Court. The Court did not ask the Solicitor General to reflect on other possible constructions of Claim 13 *not* adopted by the Federal Circuit; it paraphrased the Federal Circuit's construction and asked whether *that* construction would render the claim invalid for seeking to patent a law of nature. The Federal Circuit construed Claim 13 as claiming a scientific correlation rather than any inventive application of it. No further factual development is needed to determine that this construction cannot stand.

The United States correctly observes that the "natural relationship between elevated total homocysteine and deficiencies in the B vitamins" is unpatentable "just as the relationship between energy, mass, and the speed of light discovered by Einstein ($E=mc^2$), and the relationship between force of attraction, mass, and distance discovered by Newton (the law of gravity), are unpatentable natural phenomena." U.S. Br. 6 (citing *Diamond* v. *Chakrabarty*, 447 U.S. 303, 309 (1980)). *See Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948) (natural phenomena, "like the heat of the sun, electricity, or the qualities of metals" are "manifestations of laws of nature, free to all men and reserved exclusively to none") (cited at Pet. 18, 26). But the Solicitor General then opines that further facts may be needed to determine whether Claim 13 seeks such an impermissible monopoly. That is wrong. Under the United States' *own* reasoning, the liability imposed by the Court of Appeals is impermissible.

The Federal Circuit construed the patent as bestowing the right to prevent any doctor from merely *thinking* about a basic scientific correlation when treating patients. The court held that Claim 13 is infringed whenever a doctor looks at a homocysteine test result—no matter the reason or method for

performing the test—and *thinks* that the result might signify a vitamin deficiency (*i.e.*, "correlates"). Allowing such a claim would "wholly pre-empt" a natural principle and "in practical effect would be a patent on the [correlation] itself." *Gottschalk* v. *Benson*, 409 U.S. 63, 72 (1972). Using the United States' own example taken from this Court's precedents, if respondents were correct here, Einstein could have prevented any physicist from thinking about his famous equation simply by drafting the patent claim "test for E and correlate with mc^2" or "test for m and correlate with E/c^2."

The Solicitor General opines that Claim 13 might not seek a monopoly over a law of nature because various methods of *assaying* for homocysteine "entail significant physical or chemical alteration of a blood or fluid sample." U.S. Br. 9. But that argument ignores the fundamental fact that *Claim 13 applies regardless of how the assay is conducted.* The inventive, transformative assay method the United States describes, *id.* at 9-10, is set forth in *different* patent claims not at issue in this case—and LabCorp continues to pay royalties whenever it uses that patented method. Claim 13 asserts as private intellectual property the act of "correlating" (wholly in one's mind) *any* test result against a scientific fact.

The Solicitor General thus misses the point when he suggests that "[t]he record is * * * not well developed" as to whether the process claimed in Claim 13 includes every "practical application" of the natural relationship between homocysteine and vitamin deficiencies. *Id.* at 10 (internal quotations omitted). Claim 13 purports to patent the mental act of thinking about a test result. The record need not be developed to flesh out all of the possible ways to test or think, for they are all embraced within that claim. There are similarly many different ways to measure energy or mass, some of which might be patentable on their own, but that would not have allowed Einstein to patent a method claiming no more than "test for energy and correlate with mass times the speed of light squared." No "factual development" would

be required to determine that such a patent claim was invalid, and no further factual development is required here.[1]

The trivial requirement that an assay be conducted before "correlating" cannot transform Claim 13 into a novel invention, because the correlation itself embodies the obvious notion that a homocysteine level somehow be observed. The assaying step—which can use *any* method, patented or not—is precisely the kind of "token" activity that, under this Court's cases, cannot disguise respondents' attempt to claim a monopoly over the correlation itself. "The process itself, not merely the mathematical algorithm, must be new and useful." *Parker* v. *Flook*, 437 U.S. 584, 591 (1978). One cannot patent an unpatentable principle merely by grafting onto it a non-inventive use. *Id.* at 590. *See Funk Bros.*, 333 U.S. at 130 (a "hitherto unknown phenomenon of nature" is not patentable; only "the application of the law of nature to a new and useful end" is). Thus, "a mathematical formula does not become patentable subject matter merely by including in the claim for the formula token postsolution activity * * *." *Diehr*, 450 U.S. at 192 n.14. Unlike the patent in *Diehr*, which claimed a complex "industrial process" for molding rubber products rather than just a "mathematical formula," *id.* at 192-193, Claim 13, as construed by the Federal Circuit, involves *no* inventive process beyond the correlation itself.

"Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." *Gottschalk*, 409 U.S. at 67. Applying that principle here would *not* call into question all "patents on medical di-

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[1] Regardless, the mere *possibility* that the Court might need to remand for proceedings applying the facts to legal principles established by its decision is no basis for allowing the erroneous decision here to stand. To borrow the Solicitor General's phrase, there is "at least some possibility" (U.S. Br. 18) that such a remand may be warranted in virtually any case that reaches this Court.

agnostic methods" or "computer-related processes." U.S. Br. 14. After all, the claims of this patent asserting a particular method of testing for homocysteine are unchallenged, and LabCorp continues to pay royalties for that method. Claim 13, by contrast, seeks a monopoly over the thought processes of doctors. Invalidating that claim will not affect truly inventive diagnostic methods. To the contrary, it will advance public health by preventing respondents and others from patenting the right to prevent doctors from merely thinking about medical facts necessary for sound medical treatment.

II. THE ISSUE IS PROPERLY BEFORE THE COURT

Rather than answer the question posed by the Court, the Solicitor General spends much of his brief opining on whether the Court should, as a prudential matter, decide it. To be clear, as the United States itself acknowledges, there is no *jurisdictional* impediment to reaching this issue, which the Court has "inherent discretion" to consider. U.S. Br. 16. In any event, the basic question was posed in the petition and below and there is no reason for the Court not to reach it.

This Court will consider any question "fairly included" in the questions presented. S. Ct. R. 14.1(a). Here, the questions presented asked, *inter alia*, whether a patent "directing a party simply to 'correlat[e]' test results can validly claim a monopoly over a basic scientific relationship used in medical treatment." Pet. i. The body of the petition, moreover, extensively addressed the question posed in the Court's invitation order, citing and relying on not only *Diehr*, but other precedents to the same effect. *See, e.g.*, Pet. 18, 19, 25-26, 27, 29; *see also* Pet. Reply 6.

Rule 15.2 "admonishe[s]" respondents' counsel "to point out in the brief in opposition and not later, any perceived misstatement made in the petition," and states that "[a]ny objection to consideration of a question presented based on what occurred in the proceedings below, if the question does not go to jurisdiction, may be deemed waived unless called to the Court's attention in the brief in opposition." S. Ct. R.

15.2(a). Yet respondents' brief in opposition nowhere objects to consideration of this issue based on what occurred below or otherwise. The issue is therefore squarely before the Court. Indeed, even when the question of patentability is *not* raised by the parties, it has been settled for more than a century that courts can and should address that important issue in adjudicating a claim for patent infringement.[2]

But the question posed by this Court was also posed below. In the Court of Appeals, LabCorp expressly argued that

> [i]f the Court were to uphold this vague claim, anyone could obtain a patent on any scientific correlation—that there is a link between fact A and fact B—merely by drafting a patent claiming no more than "test for fact A and correlate with fact B," without any explanation of the testing or correlation processes. Claim 13 does no more than that. If it is upheld, CTI would improperly gain a monopoly over a basic scientific fact rather than any novel invention of its own. The law is settled that no such claim should be allowed. *See, e.g.*, *Diamond* v.

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[2] *See, e.g.*, *Hill* v. *Wooster*, 132 U.S. 693, 698 (1890) ("neither the Circuit Court nor this court can overlook the question of patentability"); *Slawson* v. *Grand St. R.R.*, 107 U.S. 649, 652 (1883) ("If letters patent are void because the device or contrivance described therein is not patentable, it is the duty of the court to dismiss the cause on that ground whether the defense be made or not. * * * Every suitor in a cause founded on letters patent should, therefore, understand that the question whether his invention is patentable or not, is always open to the consideration of the court, whether the point is raised by the answer or not."); *Smithkline Beecham Corp.* v. *Apotex Corp.*, 403 F.3d 1331, 1352-55 (Fed. Cir. 2005) (Gajarsa, J., concurring); *Howes* v. *Great Lakes Press Corp.*, 679 F.2d 1023, 1028 (2d Cir. 1982) (patentability "deals with the subject matter of patents and, as such, it is 'always open to the consideration of the court'") (citation omitted); *Barkeij* v. *Lockheed Aircraft Corp.*, 210 F.2d 1, 2 (9th Cir. 1954) ("it is the duty of the court to dismiss a patent infringement suit whenever it affirmatively appears that the patent is invalid").

> *Diehr*, 450 U.S. 175, 185 (1981) ("[e]xcluded from * * * patent protection are laws of nature, natural phenomena, and abstract ideas"); Chisum on Patents § 1.03[6].

LabCorp Ct. App. Br. at 41.

The issue also arose in the trial court; indeed, it was raised *by the court itself*. In construing Claim 13, the court held that " '[c]orrelating' is a verb, and must * * * comprise a discrete, sequential process step." A221. And it further stated

> [A]n invention is not just an idea, it is not just a mental discovery. It must combine the idea with the means of putting it into practice and producing the desired result. And so until the discovery is put into a practical form, there is no invention. There is no valid patent. * * * The Supreme Court, way back when, in [*T.H. Symington Co.* v. *National Malleable Castings Co.*, 250 U.S. 383 (1919)], said "A conception of the mind, not represented in some physical form, is not an invention." So if one takes the statement, which may very well be a wonderful new conception, that if there is an elevated level of total homocysteine and * * * that elevated level can be correlated in said body fluid with deficiency of cobalamin or folate, that is certainly a new idea, something original. But what is the * * * practical form of that? What are the actual steps? What are the discrete, sequential steps for putting into practice this new statement?

A3046-47 (*Markman* hearing transcript). As the court reiterated at trial "[b]asically, what my ruling was is that *you can't patent an idea. You have to patent an act or the test* * * *." A4662-63 (emphasis added).[3]

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[3] *See also* A3057 (trial court direction to "[t]ell me what practical steps are done to do [the correlating]? Because we know from the case law that there must be a practical form. Can't be just a mental conception. So what do you do? No. 1, No. 2, No. 3, No. 4. What do you do to correlate?"); Trial Tr., Vol. IX, at 1689 (trial court statement that "it's difficult to think you can patent an idea,

Thus, the trial court had ruled that Claim 13 would invalidly claim a monopoly over a law of nature unless "correlating" comprised an active step beyond simply thinking about the correlation, and had incorporated that requirement into its claim construction. On that premise, LabCorp consistently argued below that the patent should be construed to require evidence of this step needed to save it from invalidity, or else it would be hopelessly ill-defined. For example, in seeking a new trial or JMOL, LabCorp argued that there was no evidence that doctors engaged in a "discrete, sequential process step" as the claim construction had required to avoid the invalidity problem and, relatedly, that the patent provided no definite guidance as to how this discrete process step was to be accomplished. *See, e.g.*, LabCorp Renewed Motion for JMOL at 5 ("As interpreted by the Court, the second step of claim 13 must be 'a discrete step in a sequential process.' The Court has held that the second step must be an active step—a mental step is insufficient.") (R. 249).

The Solicitor General is therefore wrong to assert that the lower courts did not construe the claim with the inventiveness requirement in mind. U.S. Br. 17-18. The District Court initially did just that, and the Federal Circuit simply ignored the dangerous invalidity implications—specifically raised by LabCorp—of not requiring a further active step beyond thinking about the correlation. The Solicitor General says that there is "some possibility that the correlation step might be construed to entail a more involved medical diagnosis, beyond the simple mental step envisioned by the court of appeals' decision and this Court's question." *Id.* at 18. But LabCorp raised that *precise* argument in the Federal Circuit, *see* LabCorp Ct. App. Br. 23-25, 27-29, specifically informing the court that upholding such an ill-defined claim

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rather than a test. And that's what I'm afraid some of these patents do, is try to patent an idea."); *id.* at 1707 (trial court statement that "[l]ets talk about whether you really can patent an idea, though, rather than a method * * *. This is part of the argument.").

would render it invalid under *Diehr*, *id.* at 41. However, the Federal Circuit, at respondents' urging, expressly rejected the argument, wrongly construing Claim 13 to require no further step beyond rote mental application of the correlation.

Accordingly, the question whether that construction would render the patent invalid is properly and squarely before this Court, either by itself or in connection with LabCorp's other challenges to the Federal Circuit's decision.

III. CERTIORARI OR GVR IS WARRANTED

Defending the Patent and Trademark Office—which issued this defective patent in the first place—the Solicitor General urges the Court not to "overturn[ ] PTO's approach." U.S. Br. 14. Indeed, one wonders whether the Solicitor General's focus on matters outside the Court's invitation order is simply an effort to avoid review of the PTO's own practices. In any event, the Solicitor General's own reasoning shows that the case is an important one that warrants certiorari.

As the petition explains, respondents' attempt to monopolize *all* homocysteine testing is itself an issue of extraordinary national importance. The Solicitor General now admits that the case involves "a fundamentally important issue" that also potentially calls into question other patents on diagnostic methods. *Id.* at 14-15. Although truly inventive methods will be unaffected, *supra* at 5, the "PTO's approach," if allowed to stand, would in fact open the floodgates to monopolization of virtually *any* scientific correlation merely by drafting a vague "test plus correlate" claim. The Solicitor General also opines that the case implicates unresolved "tension" between this Court's decisions in *Diehr* and *Flook*, *id.* at 12, which the Federal Circuit has resolved for itself by holding that *Diehr* silently "superseded" *Flook*. *Id.* at 13. The result is the expansive view of patentability that led to the decision below. Whether or not the PTO—whose power extends as far as the patent laws—thinks that is a good idea, the admitted confusion in the law underscores the need for the Court to clarify this "fundamentally important issue."

Finally, as LabCorp anticipated in its first supplemental brief, certiorari or GVR is warranted in light of the Court's new decision in *Metro-Goldwyn-Mayer Studios Inc.* v. *Grokster, Ltd.*, 125 S. Ct. 2764 (2005). *Grokster* is the Court's first extensive examination of the law of induced infringement, which the Court held was identical in both patent and copyright law. *Id.* at 2780. The Court did not resolve the issue dividing the Federal Circuit and raised in this case—the standard for intent to induce—and certiorari is thus still warranted on that question. *See* Pet. 12-19. But just as the Court remanded *Grokster* for application of its new standard to the facts of that case, 125 S. Ct. at 2782-83, the Court should at a minimum remand this case for further consideration under that new standard. Indeed, remand is even more appropriate here. For unlike *Grokster*, which involved substantial evidence that the defendants specifically intended to encourage piracy, *id.* at 2772-74, 2780-82, the Federal Circuit found the requisite intent here based *solely* on LabCorp's dissemination of truthful medical information. The patent laws cannot allow respondents to prevent doctors from thinking about a scientific fact in treating patients, or to prevent others from informing doctors about that basic fact.

CONCLUSION

For the foregoing reasons, and those in the petition, the petition should be granted and the judgment below reversed.

Respectfully submitted,

JONATHAN S. FRANKLIN*
CATHERINE E. STETSON
JESSICA L. ELLSWORTH
HOGAN & HARTSON L.L.P.
555 Thirteenth Street, N.W.
Washington, D.C. 20004
(202) 637-5766

* Counsel of Record

Counsel for Petitioner

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No. 04-607

In the Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS, DBA LABCORP, PETITIONER

v.

METABOLITE LABORATORIES, INC., ET AL.

ON PETITION FOR A WRIT OF CERTICRARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

JAMES A. TOUPIN
General Counsel
JOHN M. WHEALAN
Deputy General Counsel
RAYMOND T. CHEN
STEPHEN WALSH
Associate Solicitors
Patent and Trademark Office
Alexandria, VA 22313

PAUL D. CLEMENT
Solicitor General
Counsel of Record
PETER D. KEISLER
Assistant Attorney General
THOMAS G. HUNGAR
Deputy Solicitor General
DARYL JOSEFFER
Assistant to the Solicitor General
ANTHONY J. STEINMEYER
JEFFREY CLAIR
Attorneys
Department of Justice
Washington, D.C. 20530-0001
(202) 514-2217

QUESTION PRESENTED

Respondent's patent claims a method for detecting a form of vitamin B deficiency, which focuses upon a correlation in the human body between elevated levels of certain amino acids and deficient levels of vitamin B. The method consists of the following: First, measure the level of the relevant amino acids using any device, whether the device is, or is not, patented; second, notice whether the amino acid level is elevated and, if so, conclude that a vitamin B deficiency exists. Is the patent invalid because one cannot patent "laws of nature, natural phenomena, and abstract ideas"? *Diamond* v. *Diehr*, 450 U.S. 175, 185 (1981).

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In the Supreme Court of the United States

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LABORATORY CORPORATION OF AMERICA HOLDINGS, DBA LABCORP, PETITIONER

v.

METABOLITE LABORATORIES, INC., ET AL.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

This brief is submitted in response to the order of this Court inviting the Solicitor General to express the views of the United States. In the view of the United States, the petition for a writ of certiorari should be denied.

STATEMENT

1. Deficiencies in two B vitamins, cobalamin and folate, can cause serious illnesses such as vascular disease, cognitive dysfunction, birth defects, and cancer. Once detected, however, a deficiency can be treated with vitamin supplements. Pet. App. 2a.

Scientific researchers at University Patents Inc. (UPI), the predecessor of respondent Competitive Technologies, Inc. (CTI), determined that elevated levels of total homocysteine, an amino acid, are closely associated with deficiencies in cobalamin or folate. UPI applied for and received a

patent on methods for assaying samples of body tissues to determine total homocysteine levels, as well as methods for diagnosing cobalamin and folate deficiency based on elevated total homocysteine. Pet. App. 2a-3a. The patent claim at issue here, claim 13 of United States Patent No. 4,940,658 (the '658 patent), identifies:

> A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> assaying a body fluid for an elevated level of total homocysteine; and
>
> correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

Id. at 3a.

CTI licensed the '658 patent to respondent Metabolite Laboratories, Inc., which in turn sub-licensed the patent to the predecessor-in-interest of petitioner Laboratory Corporation of America Holdings. Physicians ordered total homocysteine assays from petitioner, which initially performed the assays under its sub-license by using the assay method set forth in the patent. In 1998, however, petitioner began using a different assay method and stopped paying royalties to Metabolite. Respondents then filed suit against petitioner for inducing patent infringement by the physicians and for breach of contract. Pet. App. 3a-4a.

2. The district court submitted the case to a jury, which found that claim 13 of the '658 patent is valid and that petitioner willfully infringed that claim and breached its contract with Metabolite. The jury assessed damages of approximately $1 million for infringement and $3.7 million for breach of contract. The court entered judgment based on the jury verdict, denied petitioner's motion for judgment as a matter of law, doubled the jury's infringement award

based on the finding of willfulness, and entered a permanent injunction against petitioner. Pet. App. 3a-4a, 34a-39a.

3. a. The Federal Circuit affirmed. Pet. App. 1a-27a. Noting that the parties focused "solely on * * * the correlating step" of claim 13, the court of appeals stressed that it did "not address the assaying step." *Id.* at 13a & n.1. "In essence," the court held, "'correlating' means to relate the presence of an elevated total homocysteine level to either a cobalamin or folate deficiency, or both * * *, and also to relate the absence of an elevated total homocysteine level to a deficiency in neither." *Id.* at 12a.

Because "[t]he record shows that physicians order assays and correlate the results of those assays," the court of appeals held that physicians who ordered assays from petitioner after petitioner stopped making royalty payments had directly infringed the patent. Pet. App. 13a. The court further concluded that substantial evidence supports the jury's finding that petitioner intended to induce such infringement because petitioner provided total homocysteine assays to physicians and encouraged the use of such assays to detect cobalamin and folate deficiency. *Id.* at 15a.

The court of appeals rejected petitioner's contentions that claim 13 is invalid on grounds of indefiniteness, lack of written description and enablement, anticipation, and obviousness. Pet. App. 15a-21a. Because "[a] patent issued by the United States Patent and Trademark Office (PTO) bears the presumption of validity under 35 U.S.C. § 282," the court explained that "[a]n accused infringer * * * must prove patent invalidity under the clear and convincing evidentiary standard." *Id.* at 15a.

In the Federal Circuit's view, petitioner did not overcome that presumption. Because claim 13 has a discernible meaning, the court concluded that it is not indefinite. Pet. App. 16a. Similarly, the court concluded that UPI enabled

the invention by disclosing all of the necessary steps, and that the written description of the claim adequately demonstrated that the inventors possessed the invention at the time of the original filing. *Id.* at 17a-18a. Because the prior art in the record did not specifically disclose that total homocysteine is correlated with B vitamin deficiency, the court further concluded that claim 13 was neither anticipated by the prior art nor obvious. *Id.* at 18a-20a.

Finally, the court of appeals affirmed the judgment of the district court on a variety of other points not at issue here, including liability for breach of contract, enhancement of damages for infringement, and injunctive relief. Pet. App. 23a-27a. It did not determine whether the patent claims unpatentable subject matter, because petitioner had not challenged claim 13's validity on that ground.

b. Judge Schall concurred in part and dissented in part. Pet. App. 28a-33a. He "agree[d] with the majority's conclusions with respect to validity" of the patent, but construed claim 13 more narrowly than the majority. *Id.* at 28a. Because "[t]he plain language of the claim requires 'elevated' levels of homocysteine," Judge Schall concluded that claim 13 is infringed only when a test reveals elevated levels, not when it reveals normal or low levels. *Id.* at 30a.

c. The court of appeals denied a petition for rehearing and rehearing en banc. Pet. App. 40a-41a.

DISCUSSION

This Court requested the views of the United States limited to the question whether claim 13 of the '658 patent is "invalid because one cannot patent 'laws of nature, natural phenomena, and abstract ideas.'" 125 S. Ct. 1413 (2005) (quoting *Diamond* v. *Diehr*, 450 U.S. 175, 185 (1981)). Claim 13 describes more than a natural phenomenon, as it does not merely recite a natural relationship between ele-

vated total homocysteine and deficiencies in the B vitamins, but also claims a diagnostic method based on that relationship—assaying for total homocysteine in order to determine cobalamin or folate deficiency. Whether that application of the natural relationship is patentable may depend in part on facts that are not well developed in the record, in large measure because the validity of claim 13 under the natural phenomenon doctrine was neither pressed nor passed upon below. The petition should therefore be denied.

A. THE PATENT CLAIM APPEARS TO INVOLVE AN UNPATENTABLE NATURAL PHENOMENON

1. The scope of patentable subject matter is generally quite broad. "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor" if the other conditions for patentability, such as novelty and non-obviousness, are satisfied. 35 U.S.C. 101. Thus, this Court has noted that "Congress intended statutory subject matter to 'include anything under the sun that is made by man.'" *Diehr*, 450 U.S. at 182 (quoting S. Rep. No. 1979, 82d Cong., 2d Sess. 5 (1952), and H.R. Rep. No. 1923, 82d Cong., 2d Sess. 6 (1952)).

"Excluded from such patent protection," however, are "laws of nature, natural phenomena, and abstract ideas." *Diehr*, 450 U.S. at 185; accord, *e.g.*, *Diamond* v. *Chakrabarty*, 447 U.S. 303, 309 (1980); *Parker* v. *Flook*, 437 U.S. 584, 589 (1978); *Gottschalk* v. *Benson*, 409 U.S. 63, 67-68 (1972); *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948); *Mackay Radio & Tel. Co.* v. *Radio Corp. of Am.*, 306 U.S. 86, 94 (1939). "A principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented, as no one can claim in either of them an exclu-

sive right." *Le Roy* v. *Tatham*, 55 U.S. (14 How.) 156, 175 (1853); see *Rubber-Tip Pencil Co.* v. *Howard*, 87 U.S. (20 Wall.) 498, 507 (1874); *O'Reilly* v. *Morse*, 56 U.S. (15 How.) 62, 116 (1853). Instead, such "manifestations of laws of nature" are "part of the storehouse of knowledge," "free to all men and reserved exclusively to none." *Funk*, 333 U.S. at 130; see *Benson*, 409 U.S. at 67 ("Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work.").

Thus, "a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter" under Section 101. *Chakrabarty*, 447 U.S. at 309. "Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity." *Ibid.* Nor can one patent "a novel and useful mathematical formula," *Flook*, 437 U.S. at 585; electromagnetism or steam power, *Morse*, 56 U.S. (15 How.) at 113-114; or "[t]he qualities of * * * bacteria, * * * the heat of the sun, electricity, or the qualities of metals," *Funk*, 333 U.S. at 130; see *Le Roy*, 55 U.S. (14 How.) at 175.

2. Claim 13 appears to *involve* such a natural phenomenon, because it asserts and relies on the existence of a naturally occurring correlation between elevated levels of total homocysteine and deficiencies in cobalamin or folate. The asserted natural relationship between elevated total homocysteine and deficiencies in the B vitamins appears to be an unpatentable "principle in natural philosophy or physical science," *Morse*, 56 U.S. (15 How.) at 116, just as the relationship between energy, mass, and the speed of light discovered by Einstein ($E=mc^2$), and the relationship between force of attraction, mass, and distance discovered by Newton (the law of gravity), are unpatentable natural phenomena. See *Chakrabarty*, 447 U.S. at 309. To the ex-

tent that the relationship is no more than an observable, naturally occurring fact of human physiology, it is also analogous to observations of the properties of bacterial strains and metals, which this Court has held to be unpatentable. See *Funk*, 333 U.S. at 130.

B. THE RECORD MAY NOT BE SUFFICIENTLY DEVELOPED TO PERMIT AN ASSESSMENT OF THE PATENT CLAIM'S VALIDITY

Determining whether claim 13 *involves* a phenomenon of nature is only the beginning of the inquiry, however, because "[i]t is now commonplace that an *application* of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection." *Diehr*, 450 U.S. at 187; accord *Flook*, 437 U.S. at 590 ("[A] process is not unpatentable simply because it contains a law of nature."); *Benson*, 409 U.S. at 67; *Funk*, 333 U.S. at 130; *Mackay*, 306 U.S. at 94; *Rubber-Tip Pencil Co.*, 87 U.S. (20 Wall.) at 507; *Le Roy*, 55 U.S. (14 How.) at 175. "[A] claim drawn to subject matter otherwise statutory does not become non-statutory simply because it uses a mathematical formula" or other scientific principle. *Diehr*, 450 U.S. at 187. Instead, "[w]hile a scientific truth, or the mathematical expression of it, is not a patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be." *Id.* at 188 (quoting *Mackay*, 306 U.S. at 94).

1. This case involves a patent on a process, as opposed to a product, and "[t]he line between a patentable 'process' and an unpatentable 'principle' is not always clear." *Flook*, 437 U.S. at 589. In general, however, the "[t]ransformation and reduction of an article 'to a different state or thing' is the clue to the patentability of a process claim that does not include particular machines." *Diehr*, 450 U.S. 184 (quoting

Benson, 409 U.S. at 70); see *Flook*, 437 U.S. at 588-589 & n.9; *Cochrane* v. *Deener*, 94 U.S. 780, 787-788 (1876).

Even when a patent purports to apply a phenomenon of nature as part of a patentable process, the inquiry is not over. "The rule that the discovery of a law of nature cannot be patented rests, not on the notion that natural phenomena are not processes, but rather on the more fundamental understanding that they are not the kind of 'discoveries' that the statute was enacted to protect." *Flook*, 437 U.S. at 593. Thus, it is necessary "to determine what type of discovery is sought to be patented." *Ibid.*

For example, the prohibition against patenting natural phenomena "cannot be circumvented by attempting to limit the use of [a law of nature] to a particular technological environment," *Diehr*, 450 U.S. at 191, such as by attempting to patent the use of electromagnetism in communications, or the use of steam power in transportation. *Morse*, 56 U.S. (15 How.) at 112-113; accord *Flook*, 437 U.S. at 590, 594. Nor can one patent a process that comprises every "substantial practical application" of a law of nature, because such a patent "in practical effect would be a patent on the [law of nature] itself." *Benson*, 409 U.S. at 71-72; cf. *Diehr*, 450 U.S. at 187 (stressing that patent applicants in that case did "not seek to pre-empt the use of [an] equation," but instead sought only to "foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process").

Such limitations on process patents are important because without them, "a competent draftsman [could] evade the recognized limitations on the type of subject matter eligible for patent protection." *Diehr*, 450 U.S. at 192; accord *Flook*, 437 U.S. at 590, 593. Only "when a claim containing a [law of nature] implements or applies that [law] in a structure or process which, when considered as a whole,

is performing a function which the patent laws were designed to protect," does "the claim satisf[y] the requirements of § 101." *Diehr*, 450 U.S. at 192.

2. The record is not sufficiently developed to permit comprehensive consideration of the question whether claim 13 satisfies the subject matter requirements of Section 101. "In determining the eligibility of respondents' claimed process for patent protection under § 101, their claims must be considered as a whole." *Diehr*, 450 U.S. at 188; accord *Flook*, 437 U.S. at 594 & n.16. Taken as a whole, claim 13 sets forth a two-step method comprised of assaying a sample of bodily fluid for total homocysteine and then using the results of that assay in determining whether the sample indicates a cobalamin or folate deficiency.

Because petitioner did not argue below that claim 13 attempts to claim non-patentable subject matter and is therefore invalid under Section 101 (see pp. 15-16, *infra*), the courts did not focus on the term "assay" or otherwise address claim 13 "as a whole." Indeed, the lower courts did not interpret the claim term "assay" at all. See Pet. App. 13a. Assaying is, however, generally understood to refer to "[t]he quantitative analysis of a substance to determine the proportion of some valuable or potent constituent." *Larousse Dictionary of Science and Technology* 64 (Peter M.B. Walker ed., 1995). It is likely that all known methods of conducting such analysis of total homocysteine entail significant physical or chemical alteration of a sample of blood or other bodily fluid. The patent at issue here, for example, sets forth specific methods of assaying for homocysteine that entail substantial physical and chemical manipulation of a sample through the following steps:

1. preparing serum from a blood sample;
2. adding a reducing reagent and heating the serum;
3. separating and discarding proteins from the serum, in part through centrifuging;
4. removing salt ions by running the sample through an ion exchange column;
5. collecting and drying the fractions that contain homocysteine;
6. adding N-methyl-N-(t-butyldimethylsilyl) trifluoroacetamide to the sample;
7. centrifuging and drying the sample; and
8. injecting the sample into a gas chromatograph with a mass spectrometer.

C.A. App. 914-915. Other assay methods described in the record likewise require substantial chemical processing. See Pl. Tr. Exh. 205; Def. Tr. Exhs. JP, BT. Considered as a whole, therefore, the claimed process appears to entail the "[t]ransformation and reduction of an article 'to a different state or thing,'" *Benson*, 409 U.S. at 70, but the record is not fully developed on that point, and it is at least possible that other methods of measuring total homocysteine levels would not involve the transformation of matter.

The record is also not well developed on the question whether the process claimed in claim 13 comprises every "substantial practical application" of the natural relationship between elevated total homocysteine and deficiencies in the B vitamins. See *Benson*, 409 U.S. at 71-72; p. 8, *supra*. Indeed, there appears to be nothing in the record that directly addresses the question whether there are other practical applications that qualify as "substantial" within the meaning of *Benson*.

3. If the claim necessarily involved the transformation of matter and did not comprise every substantial practical application of a natural phenomenon, the next question would be whether compliance with those criteria alone would suffice to bring the claim within the scope of patentable subject matter under Section 101.

a. At least before this Court decided *Diehr*, *supra*, the answer would appear to have been no. In *Flook*, this Court held that "the discovery of [a natural] phenomenon cannot support a patent unless there is some other *inventive* concept in its application." 437 U.S. at 594 (emphasis added). *Flook* therefore held that an applicant could not patent a process that consisted of three steps: measuring temperature during a catalytic conversion process; calculating an "alarm limit" pursuant to a mathematical algorithm based in part on the temperature; and updating the alarm limit based on the result of that calculation. *Id.* at 585. Although that process "implement[ed] a principle in some specific fashion," it was unpatentable because the natural algorithm—"[t]he only novel feature of the method"—merely "reveals a relationship that has always existed." *Id.* at 585, 593 & n.15. This Court explained that "once th[e] algorithm is assumed to be within the prior art, the application, considered as a whole, contains no patentable invention." *Id.* at 594. Instead, the patent claim was merely "comparable to a claim that the formula $2\pi r$ can be usefully applied in determining the circumference of a wheel." *Id.* at 595.

Under *Flook*, therefore, an applicant could not claim patentable subject matter merely by setting forth a method that transformed matter and that did not claim all substantial practical applications of a natural phenomenon. Instead, the claim, considered as a whole, also had to contain some inventive aspect other than the natural phenomenon itself. 437 U.S. at 594-595 & n.16; accord *Funk*, 333 U.S. at

132 (holding patent on mixed inoculant invalid because "once nature's secret of the non-inhibitive quality of certain strains of the species of Rhizobium was discovered, the state of the art made the production of a mixed inoculant a simple step * * * not the product of invention").

b. This Court's subsequent decision in *Diehr*, *supra*, appears to have taken a broader view of patentable subject matter than some language in *Flook* might have been read to suggest, and it has been viewed as being in tension with *Flook*. In *Diehr*, this Court held that although one cannot patent a mathematical formula, a multi-step process for curing synthetic rubber that made use of such a formula was patentable. 450 U.S. at 186-187. The Court explained that "when a claim containing a mathematical formula implements or applies that formula in a structure or process which, when considered as a whole, is performing a function which the patent laws were designed to protect (*e.g.*, transforming or reducing an article to a different state or thing), then the claim satisfies the requirements of § 101." *Id.* at 192. In so holding, the Court stated that the novelty of an invention is "of no relevance in determining whether the subject matter of a claim falls within the § 101 categories of potentially patentable subject matter." *Id.* at 188-189; see *id.* at 190 ("[W]hether a particular invention is novel is 'wholly apart from whether the invention falls into a category of statutory subject matter.'") (quoting *In re Bergy*, 596 F.2d 952, 961 (C.P.P.A. 1979), vacated as moot, 444 U.S. 1028 (1980)).

The *Diehr* Court reconciled its analysis with *Flook* on the ground that *Flook* "stand[s] for no more than [the] long-established principles" that "laws of nature, natural phenomena, and abstract ideas" are not patentable subject matter. 450 U.S. at 185. The Court stated that *Flook* involved an attempt to patent only a mathematical formula,

because although the patent claims were drawn to a method for computing an alarm limit based on several variables, they did not explain how to determine those variables, and did not disclose other matters regarding the use of the formula. *Id.* at 186-187 & n.10. Although the claimed method in *Flook* involved the "insignificant post-solution activity" of triggering an alarm based on the result of the calculations, the *Diehr* Court concluded that such activity "will not transform an unpatentable principle into a patentable process." *Id.* at 191-192 & n.14. By contrast, the patent applicants in *Diehr* did not seek to patent a mathematical formula or other natural phenomenon. Rather, they sought "patent protection for a process of curing synthetic rubber." *Id.* at 187.

c. The Federal Circuit's predecessor was strongly critical of *Flook*'s reasoning even before this Court decided *Diehr*. See *In re Bergy*, 596 F.2d at 965-966; see also *Diehr*, 450 U.S. at 204 (Stevens, J., dissenting) (observing that "in general *Flook* was not enthusiastically received by that court"); *id.* at 205 (stating that the lower court's reading of *Flook*, "although entirely consistent with the lower court's expansive approach to § 101 during the past 12 years[,] trivializes the holding in *Flook*"). The Federal Circuit later concluded that *Flook* had been "in part superseded" by *Diehr*. *Arrhythmia Research Tech., Inc.* v. *Corazonix Corp.*, 958 F.2d 1053, 1057 n.4 (1992); see *AT&T* v. *Excel Communications, Inc.*, 172 F.3d 1352, 1356 (Fed. Cir.) (stating that *Diehr* "expressly limited" *Flook*, and thereby "supported and enhanced th[e] effort" of the Federal Circuit's predecessor to "overturn[] some of the earlier limiting principles regarding § 101"), cert. denied, 528 U.S. 946 (1999).

According to the Federal Circuit, *Diehr* and *Flook* taken together stand only for "a rather straightforward

concept, namely, that certain types of mathematical subject matter, standing alone, represent nothing more than *abstract ideas* until reduced to some type of practical application, and thus that subject matter is not, in and of itself, entitled to patent protection." *In re Alappat*, 33 F.3d 1526, 1543 (1994). At least in the context of mathematical algorithms, therefore, the Federal Circuit has concluded that the proscription against patenting natural phenomena "is narrowly limited to mathematical algorithms *in the abstract*." *AT&T*, 172 F.3d at 1356 (emphasis added). More broadly, the Federal Circuit views an invention as not patentable if "the claimed subject matter as a whole is a disembodied mathematical concept representing nothing more than a 'law of nature' or an 'abstract idea,'" but views an invention as generally patentable if "the mathematical concept has been reduced to some practical application rendering it 'useful.'" *Id.* at 1357; accord *Alappat*, 33 F.3d at 1553-1554; *State St. Bank & Trust Co.* v. *Signature Fin. Group, Inc.*, 149 F.3d 1368, 1373 (Fed. Cir. 1998), cert. denied, 525 U.S. 1093 (1999).

Since this Court decided *Diehr* almost 25 years ago, PTO has generally followed the Federal Circuit's understanding that *Diehr* substantially limited *Flook*, and has issued numerous patents based on that understanding—including patents on medical diagnostic methods, other types of diagnostic and testing procedures, and computer-related processes. A decision overturning PTO's approach could call into question a substantial number of patent claims and undermine the settled expectations of numerous participants in technology-based industries. As explained below, this case does not provide an appropriate

vehicle for examining such a fundamentally important issue.*

C. THIS CASE DOES NOT PROVIDE AN APPROPRIATE VEHICLE FOR RESOLVING THE COURT'S QUESTION

This case does not provide a suitable vehicle for considering the question posed by this Court because petitioner failed either to preserve that issue in the lower courts or to develop a complete record, and the correct resolution of this case might not turn on the choice of legal standard in any event.

1. a. Petitioner did not challenge the validity of claim 13 under the natural phenomenon doctrine in either of the lower courts, and neither of those courts addressed the question. Indeed, petitioner did not mount any challenge, under any theory, to the patentability of the claimed subject matter under Section 101. Instead, petitioner argued that claim 13 is invalid for indefiniteness, lack of written description, lack of enablement, anticipation, and obviousness. Pet. Corr. C.A. Br. 38-52.

In the court of appeals, petitioner did allude to the natural phenomenon argument in the course of arguing that claim 13 is indefinite because it does not describe the "correlation" step with sufficient specificity. Pet. Corr. C.A. Br.

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* Of course, many medical and diagnostic procedures are patentable under the reasoning of either *Flook* or *Diehr* because they apply laws of nature in inventive ways. For example, the patent at issue here claims a series of assay methods whose validity has never been challenged, in part because they provide inventive ways of measuring substances in bodies. See C.A. App. 929. The number of patent claims that would be invalidated by a reversal of the Federal Circuit's understanding of *Flook* and *Diehr* is difficult to predict, and would depend in part on the rule of law adopted by this Court. At a minimum, however, a paradigm shift in the way PTO and the lower courts have viewed *Diehr* would engender substantial uncertainty.

41. In particular, petitioner noted in passing that if its indefiniteness challenge were rejected, respondent CTI "would improperly gain a monopoly over a basic scientific fact rather than any novel invention of its own. The law is settled that no such claim should be allowed." *Ibid.* (citing *Diehr*, 450 U.S. at 185). Petitioner advanced that cursory argument solely in support of its indefiniteness challenge, however, not as a separate challenge under Section 101.

Moreover, respondents correctly noted in their brief below that even if petitioner were to contend that "the claim is directed toward non-patentable subject matter under § 101 * * * [s]uch an argument is an affirmative defense that is waived as never pleaded and never tried." Resp. C.A. Br. 71. Petitioner did not respond to that point (or otherwise pursue a claim under the natural phenomenon doctrine) in its reply brief, and the court of appeals understandably refrained from addressing the issue. Because the natural phenomenon question was neither properly presented nor passed upon below, review should be denied. See, *e.g.*, *Adarand Constructors, Inc.* v. *Mineta*, 534 U.S. 103, 109 (2001); *Glover* v. *United States*, 531 U.S. 198, 205 (2001).

b. To be sure, this Court has inherent discretion to overlook petitioner's failure to raise the issue in the lower courts, particularly in light of the fact that the brief in opposition does not call the Court's attention to the waiver. See Sup. Ct. R. 15.2. Respondents should not, however, be faulted for failing to raise a waiver objection to an issue that petitioner had not squarely raised. The petition raised the natural phenomenon issue only indirectly, as support for the claims that petitioner should not have been held liable for induced infringement and that the patent is indefinite, insufficiently described, and non-enabling. See Pet. 18, 23-26. Because the petition did not raise an independent claim

resting on the natural phenomenon doctrine, respondents should not be charged with waiving their procedural objections to such a claim.

2. Moreover, because the parties did not litigate the natural phenomenon issue below, the record is not well developed on the questions relevant to resolving that issue. As a result, it may not be possible to determine whether claim 13 is valid, or even to determine whether the choice of legal standard would ultimately matter in this case.

The patent is entitled to a presumption of validity, and petitioner bears the burden of rebutting that presumption with clear and convincing evidence. See 35 U.S.C. 282; Pet. App. 15a-16a. The record does not adequately address multiple issues potentially relevant to claim 13's validity under Section 101, including whether assaying for total homocysteine necessarily entails the transformation and reduction of an article to a different state or thing, and whether the claimed process impermissibly comprises every substantial practical application of the natural relationship between elevated total homocysteine and deficiencies in the B vitamins. See pp. 9-10, *supra*. If the latter question were answered in the affirmative, for example, claim 13 would be invalid under any reading of this Court's precedents. See *id.* at 8.

The record also may not be fully developed on the question whether the patent claim involves an inventive aspect other than a natural phenomenon. If it does involve such an aspect and the other requirements discussed above are satisfied, it is valid even under *Flook*, regardless of whether or to what extent *Diehr* limited *Flook*.

Significantly, the question whether the patent claim involves an inventive aspect other than a natural phenomenon could conceivably depend in part on the construction of the claim, and the lower courts did not construe the claim

with that concern in mind. Although courts will not rewrite patents to preserve their validity, truly ambiguous patents are construed so as to preserve their validity in appropriate cases. *Liebel-Flarsheim Co.* v. *Medrad, Inc.*, 358 F.3d 898, 911 (Fed. Cir.), cert. denied, 125 S. Ct. 316 (2004). Thus, if petitioner had relied on *Flook*'s inventiveness requirement, the parties and the courts might have approached the claim construction exercise differently.

For example, the question posed by this Court assumes that the patent claim requires only that one determine a person's total homocysteine level, and then "notice whether [that] level is elevated and, if so, conclude that a vitamin B deficiency exists." 125 S. Ct. at 1413. That interpretation of the patent claim is consistent with the Federal Circuit's holding that the claim term "correlate" means "to relate the presence of an elevated total homocysteine level to either a cobalamin or folate deficiency, or both * * *, and also to relate the absence of an elevated total homocysteine level to a deficiency in neither." Pet. App. 12a; see *id.* at 8a ("The claim only requires association of homocysteine levels with vitamin deficiencies.").

As petitioner has argued (Pet. 19 n.11), however, a total homocysteine test, by itself, may not be sufficient to determine cobalamin or folate deficiency. Instead, the patent specification appears to contemplate that additional testing could occur. See C.A. App. 911. The specification explains that although elevated total homocysteine may indicate either cobalamin or folate deficiency, additional testing can reveal *which* of the B vitamins is deficient. See *ibid.* Thus, there is at least some possibility that the correlation step might be construed to entail a more involved medical diagnosis, beyond the simple mental step envisioned by the court of appeals' decision and this Court's question.

If so, the argument that the patent claim entails an inventive aspect other than a natural phenomenon would be strengthened. But because of *petitioner's* failure to rely on *Flook*'s inventiveness requirement below (or to raise any objection to patentability under Section 101), *respondents* had no incentive to argue in favor of a limiting construction of the patent, and the lower courts had no occasion to determine whether the patent could or should be read narrowly in light of that consideration. That failure to develop the contours of the claim in the context of the natural phenomenon issue is significant. As *Flook* explained and the dissent in *Diehr* repeatedly observed, the critical starting point in determining the validity of a claim for purposes of the natural phenomenon doctrine "is an understanding of what the inventor claims to have discovered." *Diehr*, 450 U.S. at 205 (Stevens, J., dissenting); accord *id.* at 193-194; *Flook*, 437 U.S. at 593 (noting that it is necessary "to determine what type of discovery is sought to be patented").

To be sure, the construction of claim 13 might not ultimately be relevant to its validity, depending upon both the rule of law applied by this Court and the outcome of full-fledged claim construction proceedings undertaken with an eye toward the considerations discussed above. But if this Court were to consider reevaluating almost a quarter-century of administrative practice and lower court jurisprudence, it should do so based on a full record in a case where the issue was properly raised, litigated, and decided below.

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted.

JAMES A. TOUPIN
General Counsel
JOHN M. WHEALAN
Deputy General Counsel
RAYMOND T. CHEN
STEPHEN WALSH
Associate Solicitors
Patent and Trademark Office

PAUL D. CLEMENT
Solicitor General
PETER D. KEISLER
Assistant Attorney General
THOMAS G. HUNGAR
Deputy Solicitor General
DARYL JOSEFFER
Assistant to the Solicitor General
ANTHONY J. STEINMEYER
JEFFREY CLAIR
Attorneys

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IN THE

Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS (doing business as LabCorp),

Petitioner,

v.

METABOLITE LABORATORIES, INC. and COMPETITIVE TECHNOLOGIES, INC.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

JOINT APPENDIX
(Volume I of II)

JONATHAN S. FRANKLIN*
CATHERINE E. STETSON
JESSICA L. ELLSWORTH
HOGAN & HARTSON L.L.P.
555 Thirteenth Street, N.W.
Washington, D.C. 20004
(202) 637-5766

Counsel for Petitioner

GLENN K. BEATON*
GIBSON, DUNN & CRUTCHER LLP
1800 California Street
Denver, Colorado 80202
(303) 298-5773

(Additional Counsel for Respondents on Inside Cover)

Counsel for Respondents

* Counsel of Record

PETITION FOR CERTIORARI FILED NOVEMBER 3, 2004
CERTIORARI GRANTED NOVEMBER 2, 2005

Additional Counsel for Respondents:

MIGUEL A. ESTRADA
MARK A. PERRY
GIBSON, DUNN & CRUTCHER LLP
1050 Connecticut Avenue, N.W.
Washington, D.C. 20036
(202) 955-8500

MARK A. LEMLEY
KEKER & VAN NEST LLP
710 Sansome St.
San Francisco, CA 94111
(415) 391-5400

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Defendant's Ex. AH, Competitive Technologies Press Release #1 (Jan. 5, 1999) 312

Defendant's Ex. AI, Competitive Technologies Press Release #2 (Jan. 5, 1999) 315

Defendant's Ex. AM, Hollowell et al., "Homocystinuria and Organic Aciduria in a Patient with Vitamin B-12 Deficiency" (Dec. 27, 1969) 318

Defendant's Ex. AW, Grieco, "Homocystinuria: pathogenic mechanisms" (Mar. - Apr. 1977) 320

Defendant's Ex. BA, Higginbottom et al., "A Syndrome of Methylmalonic Aciduria, Homocystinuria, Megaloblastic Anemia and Neurologic Abnormalities in a Vitamin B12-Deficient Breast-Fed Infant of a Strict Vegetarian" (Aug. 17, 1978) 321

Defendant's Ex. BE, Wilcken et al., "Homocysteine in the plasma of renal transplant recipients: ef-

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fects of cofactors for methionine metabolism" (1981) 323

Defendant's Ex. BF, Hoey et al., "Vitamin B12 deficiency in a breastfed infant of a mother with pernicious anaemia" (Aug. 1982) 325

Defendant's Ex. BQ, Brattstrom et al., "Moderate Homocystinuria—A Possible Risk Factor for Arteriosclerotic Cerebrovascular Disease" (Nov.-Dec. 1984) 328

Defendant's Ex. BU, Brattstrom et al., "Folic Acid Responsive Postmenopausal Homocysteinemia" (Nov. 1985) 330

Defendant's Ex. CN, Letter from S. Stabler to Dr. Malinow (Jan. 5, 1990) 333

Defendant's Ex. IJ, Stabler, "Hyperhomocysteinemia: A Common and Treatable Cause of Vascular Disease and Neural Tube Defects" (Sept. 13, 1995) 335

Defendant's Ex. JB, Refsum et al., "Homocysteine and Vascular Disease" (1998) 338

Defendant's Ex. JC, AHA Science Advisory, "Homocyst(e)ine, Diet, and Cardiovascular Diseases" (1999), and web version of advisory 351

Defendant's Ex. LT, Example of LabCorp patient report for single homocysteine test (Mar. 29, 2000) 357

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SUPPLEMENTAL APPENDIX

United States Patent No. 4,940,658 (July 10, 1990)

The appendix to the petition for certiorari contains the following material which is omitted from the Joint Appendix:

Appendix A:

Opinion of the U.S. Court of Appeals for the Federal Circuit dated June 8, 2004 ..... 1a

Appendix B:

Order of the U.S. District Court for the District of Colorado dated November 19, 2002 ..... 34a

Appendix C:

Order of the U.S. Court of Appeals for the Federal Circuit Denying Rehearing and Rehearing En Banc dated August 5, 2004 ..... 40a

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

No. 03-1120

METABOLITE LABORATORIES, INC.
and COMPETITIVE TECHNOLOGIES, INC.,
Plaintiffs-Appellees,

v.

LABORATORY CORPORATION OF AMERICA
HOLDINGS (doing business as LabCorp),
Defendant-Appellant.

DOCKET ENTRIES

DATE	FILINGS – PROCEEDINGS
2/19/03	CORRECTED BRIEF for Appellant Laboratory Corporation of America Holdings. By Laboratory Corporation (Appellant). Served by mail on 3/12/2003. Filed on 2/19/2003. (Non-confidential)
4/21/03	BRIEF for Appellees. By Metabolite Laboratories, Inc. & Competitive Technologies, Inc. (Appellees). Served by mail on 4/21/2003. Filed on 4/21/2003. (Non-confidential)
5/8/03	REPLY BRIEF for Appellant Laboratory Corporation of America Holdings (d/b/a LabCorp). By Laboratory Corporation of America (d/b/a LabCorp) (Appellant). Served by mail on 5/8/2003. Filed on 5/8/2003. (Non-confidential)

5/15/03	JOINT APPENDIX (5 volumes). By Laboratory Corporation of America Holdings (Appellant). Served by mail on 5/15/2003. Filed on 5/15/2003. (Non-confidential)
6/30/03	SUPPLEMENTAL APPENDIX. By Metabolite Technologies, Inc. (Appellant). Served by mail on 6/9/2003. Filed on 6/30/2003. (Non-confidential)
11/5/03	ORAL ARGUMENT DATE / Calendared
6/8/04	DISPOSITION: AFFIRMED; by PANEL
8/12/04	MANDATED

U.S. DISTRICT COURT
DISTRICT OF COLORADO (DENVER)

CIVIL DOCKET FOR CASE #: 1:99-cv-00870-ZLW-CBS

METABOLITE LABORATORIES, INC.,
a Colorado corporation, and

COMPETITIVE TECHNOLOGIES, INC.,
a Delaware corporation,

Plaintiffs,

v.

LABORATORY CORPORATION OF AMERICA HOLDINGS (d/b/a LABCORP),
a Delaware corporation,

Defendant.

DOCKET ENTRIES

DATE	NO.	PROCEEDINGS
05/04/1999	1	COMPLAINT (Summons(es) issued); jury demand (former empl) (Entered: 05/05/1999)
07/19/1999	3	AMENDED COMPLAINT [1-1] by plaintiff; jury demand (former empl) (Entered: 07/20/1999)
07/20/1999	5	RETURN OF SERVICE of Summons and Complaint upon / by defendant Laboratory Corp Amer on 7/19/99 (former empl) (Entered: 07/22/1999)

08/30/1999	11	ANSWER to complaint [3-1] and COUNTERCLAIM; jury demand by defendant Laboratory Corp Amer against plaintiff (former empl) (Entered: 09/01/1999)
09/15/1999	12	REPLY TO COUNTERCLAIM [11-2] by counter-defendant Metabolite Labs Inc, counter-defendant Competitive Tech Inc (former empl) (Entered: 09/16/1999)
01/31/2000	31	Unopposed MOTION by plaintiff to file second amended cmp (former empl) (Entered: 02/01/2000)
01/31/2000		Tendered Second Amd Cmp submitted by plaintiff re: motion to file second amended cmp [31-1] (former empl) (Entered: 02/01/2000)
01/31/2000	32	MOTION by defendant Laboratory Corp Amer to file under seal mtn for leave to amend answer/cntclms (former empl) (Entered: 02/01/2000)
01/31/2000	33	MOTION by defendant Laboratory Corp Amer for leave to amend answer and cntclms (filed under seal) (former empl) (Entered: 02/01/2000)
02/02/2000	34	MINUTE ORDER : by Judge Zita L. Weinshienk granting motion to file second amended cmp [31-1] and clerk to file stamp tendered second amd cmp (cc: all counsel) ; entry date : 2/3/00 (former empl) (Entered: 02/03/2000)
02/02/2000	35	Second AMENDED COMPLAINT by plaintiff; jury demand; adding defendant Peter Wentz (former empl) (Entered: 02/03/2000)

02/14/2000	41	REPLY TO amended COUNTER-CLAIM [11-2] by counter-defendant (former empl) (Entered: 02/15/2000)
02/29/2000	49	AMENDED ANSWER [11-1] by defendant Laboratory Corp Amer; jury demand (gms) (Entered: 10/17/2001)
02/29/2000	49	AMENDED COUNTERCLAIM [11-2] by counter-claimant Laboratory Corp Amer (gms) (Entered: 10/17/2001)
03/03/2000	50	Third AMENDED COMPLAINT by plaintiff; jury demand (former empl) (Entered: 03/06/2000)
03/15/2000	52	ANSWER by defendant Laboratory Corp Amer to third amended complaint [50-1]; jury demand (gms) (Entered: 10/17/2001)
03/15/2000	52	AMENDED COUNTERCLAIM [11-2] to 3rd amd cmp by counterclaimant Laboratory Corp Amer (gms) (Entered: 10/17/2001)
03/28/2000	53	REPLY TO Amended COUNTER-CLAIMS [52-1] by counter-defendants Metabolite & Competitive (gms) (Entered: 10/17/2001)
07/31/2000	91	COURTROOM MINUTES by Judge Zita L. Weinshienk GRANTING motion to dismiss for lack of jurisdiction converted to motion for summary jgm [69-1]; dismissing party Peter Wentz on condition that he will be available as witness for trial; entry date: 8/9/00 Court Reporter: Kara Spitler (former empl) (Entered: 08/09/2000)

08/07/2000	87	MOTION by defendant Laboratory Corp Amer for summary judgment (gms) (Entered: 08/07/2000)
08/07/2000	88	Memorandum (BRIEF) by defendant Laboratory Corp Amer in support of motion for summary judgment [87-1] (gms) (Entered: 08/07/2000)
08/07/2000	89	APPENDIX filed by defendant Laboratory Corp Amer to motion for summary judgment [87-1] (gms) (Entered: 08/07/2000)
08/07/2000	90	MOTION by plaintiffs for summary judgment on patent infringement claim against deft Lab Corp of Amer Hldgs (former empl) (Entered: 08/08/2000)
08/07/2000	92	ORDER OF DISMISSAL by Judge Zita L. Weinshienk: GRANTING motion to dismiss for lack of jurisdiction converted to motion for summary jgm [69-1]; DISMISSING party Peter Wentz on condition that he will be available as witness on trial (cc: all counsel) entry date: 8/9/00 (former empl) (Entered: 08/09/2000)
08/14/2000	93	MINUTE ORDER : by Judge Zita L. Weinshienk setting hearing on each party's motion for summary judgment on patent infringement claim against deft Lab Corp of Amer Hldgs [90-1] & motion for summary judgment [87-1] 9:00 10/4/00. Responses to opposing party's motion is due 8/27/00, replies due 9/11/00. (cc: all counsel) ; entry date : 8/14/00 (gms) (Entered: 08/14/2000)
08/25/2000	94	Amended MINUTE ORDER : by Judge Zita L. Weinshienk regarding [93-1]

		minute order. Each party to file resp in opp to motion for sum jgm by 8/28/00 and each party may reply by 9/12/00. Setting hearing on motion for summary judgment on patent infringement claim against deft Lab Corp of Amer Hldgs [90-1] 9:00 10/4/00, setting hearing on motion for summary judgment [87-1] 9:00 10/4/00 (cc: all counsel) ; entry date: 8/25/00 (gms) (Entered: 08/25/2000)
08/28/2000	95	Memorandum (BRIEF) by defendant Laboratory Corp Amer in opposition to motion for summary judgment [90-1] (lam) (Entered: 08/28/2000)
08/28/2000	96	APPENDIX filed by defendant Laboratory Corp Amer to opposition brief [95-1] to motion for summary judgment [90-1] (lam) (Entered: 08/28/2000)
08/28/2000	97	RESPONSE by plaintiffs to motion for summary judgment [87-1] (former empl) (Entered: 08/29/2000)
09/12/2000	99	REPLY by defendant Laboratory Corp Amer to response to motion for summary judgment [87-1] (former empl) (Entered: 09/14/2000)
09/12/2000	100	APPENDIX filed by defendant Laboratory Corp Amer to motion reply [99-1] (former empl) (Entered: 09/14/2000)
09/12/2000	101	APPENDIX BI-BK filed by defendant Laboratory Corp Amer to motion reply (filed under seal) [99-1] (former empl) (Entered: 09/14/2000)
09/12/2000	102	MOTION by defendant Laboratory Corp Amer to seal appendix BI-BK to reply to

Motion for Summary Jgm. (former empl) (Entered: 09/14/2000)

09/12/2000 103 REPLY by plaintiff to response to motion for summary judgment on patent infringement claim against deft Lab Corp of Amer Hldgs [90-1] (former empl) (Entered: 09/14/2000)

10/04/2000 105 COURTROOM MINUTES by Judge Zita L. Weinshienk denying motion for summary judgment on patent infringement claim against deft Lab Corp of Amer Hldgs [90-1], denying motion for summary judgment [87-1] ; entry date : 10/6/00 Court Reporter: Paul Zuckerman (former empl) (Entered: 10/06/2000)

10/06/2000 106 ORDER by Judge Zita L. Weinshienk denying pla's motion for summaryjudgment on patent infringement claim against deft Lab Corp of Amer Hldgs [90-1], denying dft's motion for summary judgment [87-1] (cc: all counsel) ; entry date : 10/10/00 (former empl) (Entered: 10/10/2000)

11/02/2000 112 MarkmanBRIEF FILED by defendant Laboratory Corp Amer (former empl) (Entered: 11/03/2000)

11/02/2000 113 Claim Construction BRIEF FILED by defendant Laboratory Corp Amer (oversized document, placed on oversized document shelf) (former empl) Modified on 11/03/2000 (Entered: 11/03/2000)

11/09/2000 114 Claim Construction Response BRIEF FILED by plaintiffs (former empl) (Entered: 11/13/2000)

11/09/2000	115	RESPONSE by defendant Laboratory Corp Amer to plfs' claim construction brief [114-1] (former empl) (Entered: 11/13/2000)
11/16/2000	116	COURTROOM MINUTES by Judge Zita L. Weinshienk ; in court hrg/Markman Hearing held 11/16/00. Court will issue an order and state the scope of claim 13. Simultaneous cross motions for sum jgm due 1/5/01, reply briefs to these motions due 1/17/01 ; entry date : 11/21/00 Court Reporter: Paul Zuckerman (gms) (Entered: 11/21/2000)
11/21/2000	117	TRANSCRIPT of Markman Hearing on November 16, 2000 before Judge Zita L. Weinshienk (pages: 1-66) Prepared By: Paul Zuckerman (certified copy) (former empl) (Entered: 11/22/2000)
11/29/2000	118	ORDER by Judge Zita L. Weinshienk regarding [116-2] minutes. Term "detecting" in claim 13 is construed to mean "determining the existence of", "deficiency" to mean "a shortage of a substance necessary to health","elevated" to mean "raised above the normal range" and "correlating" to mean "to establish a mutual or reciprocal relationship between" (cc: all counsel) ; entry date : 11/30/00 (gms) (Entered: 11/30/2000)
01/05/2001	120	Renewed MOTION by defendant Laboratory Corp Amer for summary judgment (former empl) (Entered: 01/08/2001)
01/05/2001	121	MOTION by plaintiff Metabolite Labs Inc, plaintiff Competitive Tech Inc for

partial summary judgment (former empl) (Entered: 01/08/2001)

01/05/2001 122 APPENDIX in Support filed by defendant Laboratory Corp Amer to their renewed motion for summary judgment [120-1] (former empl) (Entered: 01/08/2001)

01/17/2001 127 RESPONSE (titled reply) by defendant Laboratory Corp Amer to pla's motion for partial summary judgment [121-1] (former empl) (Entered: 01/17/2001)

01/17/2001 128 APPENDIX S to dft's response to pla's motion for partial sum jgm, filed by defendant Laboratory Corp Amer under seal [127-1], re: motion to file under seal [126-1] (former empl) (Entered: 01/17/2001)

01/17/2001 129 RESPONSE by plaintiffs to dft's renewed motion for summary judgment [120-1] (former empl) (Entered: 01/18/2001)

01/23/2001 133 REPLY by plaintiff to dft's response to pla's motion for partial summary judgment [121-1] (titled: pla's surreply to dft's reply to pla's motion for partial sum jgm and motion to file same) (former empl) (Entered: 01/24/2001)

01/23/2001 133 MOTION by plaintiffs for leave to file surreply to dft's response to pla's motion for partial sum jgm with surreply incorporated in motion (former empl) (Entered: 01/24/2001)

02/12/2001 136 Opposition (RESPONSE) by counterclaimant Laboratory Corp Amer to motion for leave to file surreply to dft's re-

		sponse to pla's motion for partial sum jgm [133-1] (lam) (Entered: 02/14/2001)
02/22/2001	140	MOTION by Pla Metabolite Labs Inc, and Pla Competitive Tech Inc to strike from the final pre-trial order Labcorp's unpled defenses and claims and undisclosed witness (erv) (Entered: 02/27/2001)
02/22/2001	141	OBJECTIONS by Dft Laboratory Corp America and to motion to strike certain claims/defenses as set forth by Pla's in the final pre-trial order undisclosed witness [140-1] (erv) (Entered: 02/27/2001)
02/26/2001	143	FINAL PRE-TRIAL ORDER to Magistrate Judge Craig B. Shaffer (cc: all counsel) (erv) (Entered: 02/28/2001)
03/01/2001	170	COURTROOM MINUTES by Judge Zita L. Weinshienk ORDERED: 1) As to Pla's Motion for Partial Summary Judgment seeking a declaration that Claim 13 covers LabCorp's performance of the Panel Test, Ruling is reserved until the validity of Claim 13 is decided by fact-finder. ORDERED 2) DENYING motion for partial summary judgment seeking a declaration that Claim 13 covers LabCorp's performance of the Homocysteine-only test. [121-1], ORDERED 3) GRANTING Dft's motion for summary judgment seeking a declaration that Claim 13 and 33 do not cover LabCorp's performance of the Homocysteine-only test [120-1] ORDERED: 4) Dft's Motion for Summary Judgment seeking a Declaration that claim 13 and 33 are invalid is DENIED. ORDERED: 5) Pla's Motion for Partial Summary Judgment seeking a

		Declaration that Claim 18 covers LabCorp's performance of the Panel test is GRANTED. ORDERED: 6) Dfts' Motion for Summary Judgment seeking a Declaration that LabCorp does not induce infringement of Claim 13 and Claim 33 is DENIED. ORDERED: 7) Dfts' Motion for Summary Judgment on the issue of validity of Claim 13 and Claim 33 is DENIED.; entry date : 3/21/01 Court Reporter: Paul Zuckerman (erv) (Entered: 03/21/2001)
03/02/2001	144	RESPONSE by Dft Laboratory Corp Amer ("Lab Corp") to Pla's motion to strike from the final pre-trial order Labcorp's unpled defenses and claims and undisclosed witness [140-1] (erv) (Entered: 03/05/2001)
03/02/2001	145	REPLY by Pla Metabolite Labs Inc to Dfts' Objection and motion to strike from the final pre-trial order Labcorp's unpled defenses claims and undisclosed witness [140-1] (erv) (Entered: 03/05/2001)
03/06/2001	146	TRANSCRIPT of hrg on motions for Summary Judgment on 3-1-01 before Judge Zita Weinsheink, (pages: 1-23) Prepared By: Paul Zuckerman (certified copy) (erv) (Entered: 03/08/2001)
03/07/2001	147	TRANSCRIPT of Excerpts from hrg on Dft's motion to dismiss on 7/31/00 before Judge Zita Weinshienk (pages: 1-5) Prepared By: Kara Spitler (certified copy) (erv) (Entered: 03/08/2001)
03/08/2001	148	MOTION by Pla Metabolite Labs Inc,and Pla Competitive Tech Inc in

limine to restrict or exclude Dft's Expert Testimony (erv) (Entered: 03/12/2001)

03/08/2001 149 MOTION by Pla Metabolite Labs Inc, and Pla Competitive Tech Inc in limine to prevent Labcorp from introducing evidence or taking positions at trial that contradict previous admissions made by Labcorp (erv) (Entered: 03/12/2001)

03/08/2001 150 MOTION by Pla Metabolite Labs Inc, and Pla Competitive Tech Inc in limine to allow Jury view of Metabolite's assay procedures and know how (erv) (Entered: 03/12/2001)

03/08/2001 151 MOTION by Pla Metabolite Labs Inc, and Pla Competitive Tech Inc in limine to Require Labcorp to make Certain of its Employee Witnesses Available during Plas' case-in Chief (erv) (Entered: 03/12/2001)

03/08/2001 152 MOTION by Dft Laboratory Corp Amer in limine to Prevent Plas' from offering Parol Evidence re: the Patent License Agreement (erv) (Entered: 03/12/2001)

03/08/2001 153 MOTION by Dft Laboratory Corp Amer in limine to prevent Plas from referring to any alleged consequences of any mistakes in Labcorp's material (erv) (Entered: 03/12/2001)

03/08/2001 154 MOTION by Dft Laboratory Corp Amer in limine to prevent Plas from arguing or referring during Trial that Labcorp infringes or willfully infringes the 658 Patent (erv) (Entered: 03/12/2001)

03/08/2001 155 MOTION by Dft Laboratory Corp Amer in limine to Exclude Plas from making

		reference in any manner regarding Abbott indemnification and licensing issues (erv) (Entered: 03/12/2001)
03/08/2001	156	MOTION by DFT Laboratory Corp Amer in limine to exclude references to Royalty Payment issues previously resolved. (erv) (Entered: 03/12/2001)
03/08/2001	157	MOTION by Dft Laboratory Corp Amer in limine to exclude Plas from referring to any evidence regarding settlement of unrelated items (erv) (Entered: 03/12/2001)
03/13/2001	158	OBJECTIONS by defendant Laboratory Corp Amer to Pla's Trial Exhibits (erv) (Entered: 03/14/2001)
03/13/2001	159	OBJECTIONS by Plas' Metabolite Labs Inc, and Competitive Tech Inc to s' Designated exhibits. (Rule 26(a)(3) (erv) (Entered: 03/15/2001)
03/15/2001	160	RESPONSE by plaintiffs to dft's motion in limine to Exclude Plas from making reference in any manner regarding Abbott indemnification and licensing issues [155-1] (former empl) (Entered: 03/19/2001)
03/15/2001	161	RESPONSE by plaintiffs to dft Labcorp's motion in limine to prevent Plas from referring to any alleged consequences of any mistakes in Labcorp's material [153-1] (former empl) (Entered: 03/19/2001)
03/15/2001	162	RESPONSE by plaintiffs to dft's motion in limine to prevent Plas from arguing or referring during Trial that Labcorp infringes or willfully infringes the 658 Pat-

ent [154-1] (former empl) (Entered: 03/19/2001)

03/15/2001 163 RESPONSE by plaintiffs to dft's motion in limine to exclude references to Royalty Payment issues previously resolved. [156-1] (former empl) (Entered: 03/19/2001)

03/15/2001 164 RESPONSE by plaintiffs to dft's motion in limine to exclude Plas from referring to any evidence regarding settlement of unrelated items [157-1] (former empl) (Entered: 03/19/2001)

03/15/2001 165 RESPONSE by defendant Laboratory Corp Amer to pla's motion in limine to allow Jury view of Metabolite's assay procedures and know-how [150-1] (former empl) (Entered: 03/19/2001)

03/15/2001 166 RESPONSE by defendant Laboratory Corp Amer to pla's motion in limine to restrict or exclude Dft's Expert Testimony [148-1] (former empl) (Entered: 03/19/2001)

03/15/2001 167 RESPONSE by defendant to pla's motion in limine to Require Labcorp to make Certain of its Employee Witnesses Available during Plas' case-in Chief [151-1] (former empl) (Entered: 03/19/2001)

03/15/2001 168 RESPONSE by defendant to pla's motion in limine to prevent Labcorp from introducing evidence or taking positions at trial that contradict previous admissions made by Labcorp [149-1] (former empl) (Entered: 03/19/2001)

03/15/2001	169	RESPONSE by plaintiff to dft's motion in limine to Prevent Plas' from offering Parol Evidence re: the Patent License Agreement [152-1] (former empl) (Entered: 03/19/2001)
03/16/2001	171	ORDER by Judge Zita L. Weinshienk re: [121-1] Pla's Motion for Partial Sum Jgm, re: [120-1] Dfts' Motion for Sum Jgm. The matter was be[fo]re the Ct for Oral Argument. The Ct having heard the Arguments and Statements of Csl & made oral conclusions of law which are incorporated by reference as fully set forth. Accordingly, It is ORDERED: that as to Pla's Motn for Partial Sum Jgm seeking a declaration that Claim 13 covers LabCorp's performance of the Panel Test, ruling is reserved until the Validity of Claim 13 is decided by the fact-finder. It is Further Ordered that Pla's Motion for Partial Sum Jgm seeking a declaration that Claim 13 covers LabCorp's performance of the Homocysteine-only test is DENIED., It is Further Ordered that Dfts' motn for Sum Jgm seeking a declaration that Claim 13 and 33 do not cover LabCorp's performance of the Homocysteine-only test is GRANTED. It is Further Ordered that Dfts' Motn for Sum Jgm that Claim 13 and Claim 33 are invalid is DENIED. It is Further Ordered that Pla's mton for Partial Sum Jgm seeking a declaration that Claim 13 covers LabCorp's performance of the Panel Test is GRANTED. It is Further Ordered that Dft's motion for Sum Jgm seeking a declaration that LabCorp does not induce infringement of Claim 13 and Claim 33

		is DENIED. It is Further Ordered that Dfts' Motion for Partial Sum Jgm on issue of validity of Claims 13 and 33 is DENIED. (cc: all counsel) ; entry date : 3/21/01 (erv) (Entered: 03/21/2001)
03/19/2001	172	PRE-TRIAL STATUS REPORT by defendant Laboratory Corp Amer (erv) (Entered: 03/21/2001)
03/19/2001	173	STATUS REPORT by Pla Metabolite Labs Inc, Pla Competitive Tech Inc (erv) (Entered: 03/21/2001)
03/22/2001	179	COURTROOM MINUTES by Judge Zita L. Weinshienk DENYING motion in limine to Require Labcorp to make Certain of its Employee Witnesses Available during Plas' case-in Chief. It is the Cts understanding that Peter Wentz and Denise Hodge will be available. As to the other witnesses Pla wants, the attys shall confer and resolve any remaining disputes. The question of who bears the cost of travel will be decided at the end of trial. The Ct will allow LabCorp to question Mr. Wentz during Pla's case so that he will not be requires to return for Dfts case in chief. [151-1], finding the motion in limine to restrict or Dft's Expert Testimony [148-1] moot as the motion relates to Dr. Wentz, DENYING motion in limine to allow Jury view of Metabolite's assay procedures and know-how [150-1], DENYING motion to strike from the final pre-trial order Labcorp's unpled defenses and claims and undisclosed witness as follows: a) Motion to strike the unpled license defense is DENIED, b) motion to strike the

unpled statutory defense under 35 U.S.C.271(c) is DENIED, c) Motion to strike the copyright subject matter defense is DENIED, d) Motion to strike dfts declarations in their prayer for relief is DENIED as moot, in view of Dfts agreement to amend paragraph five. e) Motion to strike undisclosed witness, Dr. Kang is DENIED, f) Pla may depose Dr. Kang between now and the trial date. The parties shall meet with the Magistrate Judge after the hrg to discuss the need for additional discovery.[140-1], DENYING Pla's motion in limine to prevent Labcorp from introducing evidence or taking positions at trial that contradict previous admissions made by Labcorp [149-1], GRANTING in part and DENYING in part as follows: a) motion to strike reference to unpaid royalties for the panel of tests on pg 15 of the final pretrial order is DENIED b) Motion to strike the issue of whether claims 13 and 18 cover the panel test is DENIED. c) Motion to strike Pla's alleged claim of defense on page 16 of the final pre-trial order is DENIED. d) Motion to strike any reference in footnote 1, page 3 in the claims section of the pre-trial order is DENIED as moot, as the Ct will not consider this a stipulation. e) Dfts request to reserve its right to object to some stmts in the pretrial order they believe are not admissable at trial is GRANTED. [141-1], DENYING motion in limine to Exclude Plas from making reference in any manner regarding Abbott indemnification and licensing issues, with leave to

object at trial if appropriate [155-1], DENYING motion in limine to exclude references to Royalty Payment issues previously resolved. [156-1], DENYING motion in limine to prevent Plas from referring to any alleged consequences of any mistakes in Labcorp's material [153-1], GRANTING motion in limine to exclude Plas from referring to any evidence regarding settlement of unrelated items [157-1], [154-1] The ct reserves ruling on this motion in limine to prevent Plas from arguing or referring during Trial that Labcorp infringes or willfully infringes the 658 Patent,the parties may file a short brief on this issue. regarding [152-1] The Ct reserves ruling on this motion in limine to Prevent Plas' from offering Parol Evidence re: the Patent License Agreement, the parties may file short brief on this issue.; entry date : 4/16/01 Court Reporter: Paul Zuckerman (erv) (Entered: 04/16/2001)

03/26/2001 174 TRANSCRIPT of Trial Preparation Conference and Hrg on Motions on 3/22/01 before Judge Zita Weinshienk (pages: 1-53) Prepared By: Paul Zuckerman (certified copy) (erv) (Entered: 03/27/2001)

04/12/2001 180 ORDER by Judge Zita L. Weinshienk This matter was before the ct on 3/22/01, for oral argument on various motions in limine,objections and motions to strike. The ct heard the arguments and stmts of csl, and made oral conclusions of law which are incorporated herein by reference as if fully set forth, Accordingly, It is ORDERED that Plas' Motion in

limine to require Labcorp to make certain Of its Employee Witnesses availability during Pla's case-in-chief, file 3-8-01, is DENIED. It is the cts understanding that Peter Wentz and Denise Hodge will be available. As to the other requested witnesses, the parties shall confer and resolve any remaining disputes. It is Further ORDERED that Plas' motion in limine to restrict or exclude Dfts Expert testimony, filed 3-8-01 is DENIED. Both Steven Bent and Dr. McCully will be allowed to testify within their area of expertise only. As the motion relates to Dr. Wentz, the motion is Moot. It is Further ORDERED that Pla's motion in limine to allow Jury View of Metabolite's Assay Procedures and Know-How, filed 3-8-01, is DENIED. It is Further ORDERED that Plas' motion to strike from the final pretrial Order Labcorps Unpled Defenses and Claims and Undisclosed Witness, filed 2-22-01 is DENIED as follows: Motion to strike the license defense is DENIED;Motion to strike the statutory defense under 35 U.S.C. 271(c) is DENIED;motion to strike the copyright subject matter defense is DENIED; motion to strike Dfts declaration in their prayer for relief is DENIED as MOOT, in view of the Dfts agreement to amend paragraph five;motion to strike undisclosed witness Dr. Kang, is DENIED. Pla may depose Dr. Kang between now and the trial date. The parties shall meet with the Magistrate JUdge about the necessity for any further discovery. It is Further OR-

DERED that the Plas motion in limine to prevent Labcorp from introducing evidence or taking positions at trial that contradict previous admissions made by Labcorp,filed 3-8-01 is DENIED. It si Further ORDERED that Labcorps obj and motion to strike certian claims/defenses set forth by Plas in the final pretrial order, filed 2/22/01 is DENIED as follows: Motin to strike the issue of whether claims 13 and 18 cover the panel test is DENIED. Motion to strike reference to unpaid royalties for the panel tests on pg 16 of the final pretrial order is DENIED; motion to strike any reference in footnote 1,pg 3 in the claims section of the pretrial order is MOOT, as the ct will not consider it a stipulation.Dfts request to reserve its right to obj to some stmts in the pretrial order it believes are not admissable at trial is GRANTED. It is Further ORDERED that Dfts motion in limine to Exclude Plas from making reference in any mmanner regarding Abbott indemnifiication and Licensing issues, filed 3-8-01 is DENIED with lv to obj at trial if appropriate. It is Further ORDERED that Dfts motion in limine to prevent Plas from referring to any alleged consequences of any mistakes in Labcorps materials, filed 3-8-01 is DENIED with lv to obj at trial is appropriate. It is Further ORDERED that Dfts motion in limine to exclude Plas from referring to any evidence regarding settlement of unrelated matters filed 3-8-01 is GRANTED, subject to chg after consideration of the par-

		ties briefs on the subject. It is Further ORDERED that the ct reserves ruling as to Dft Labcorps motion in limine to prevent Plas from arguing or referring during trial that Labcorp infringes or willfully infringes the 658 patent, filed 3-8-01. It is Further ORDERED that the ct reserves ruling as to Dfts Labcorps motion in limine to prevent Plas from offering Parol Evidence regarding the patent license agreement filed 3-8-01. It is Further ORDERED that the parties may file short briefs on the following issues:1) Admissability of evidence regarding Labcorps settlement with theb govt; 2)whether the existence of metabolites license precludes argument on patent infringement, how the parol evidence rule applies to the specific facts of the case. Briefs shall not exceed 5 pgs and shall be filed on or before 5-18-01 (cc: all counsel) ; entry date : 4/17/01 (erv) (Entered: 04/17/2001)
05/17/2001		Tendered Fourth Amended Complaint submitted by plaintiff Metabolite Labs Inc, plaintiff Competitive Tech Inc re: motion to amend complaint and Jury demand [1-1] in view of results of ct ordered audit and rule 7.1 cert. [181-1] (erv) (Entered: 05/21/2001)
05/17/2001	182	Further BRIEF by Plaf in opposition to motion in limine to prevent Plas from arguing or referring during Trial that Labcorp infringes or willfully infringes the 658 Patent [154-1] (erv) (Entered: 05/21/2001)

05/18/2001	181	MOTION by Pla Metabolite Laboratories, Inc. and Competitive Tech Inc to amend complaint [1-1] in view of results of ct ordered audit and rule 7.1 cert. (erv) (Entered: 05/21/2001)
05/18/2001	183	BRIEF by defendant Laboratory Corp Amer in support of motion in limine to Prevent Plas' from offering Parol Evidence re: the Patent License Agreement [152-1] (erv) (Entered: 05/22/2001)
05/18/2001	184	BRIEF by defendant Laboratory Corp Amer in support of motion in limine to prevent Plas from arguing or referring during Trial that Labcorp infringes or willfully infringes the 658 Patent [154-1] (erv) (Entered: 05/22/2001)
05/18/2001	185	BRIEF by defendant Laboratory Corp Amer in support of motion in limine to exclude Plas from referring to any evidence regarding settlement of unrelated item: [157-1] (erv) (Entered: 05/22/2001)
05/18/2001	186	SUPPLEMENT by defendant Laboratory Corp Amer to brief re: Parol evidence rule [183-1], to motion in limine to Prevent Plas' from offering Parol Evidence re: the Patent License Agreement [152-1] (erv) (Entered: 05/22/2001)
05/18/2001	187	SUPPLEMENT (Further Brief) by Pla Opposing Labcorp's motion to exclude evidence of $187 Million Fraud settlement (erv) (Entered: 05/23/2001)
05/25/2001	193	MINUTE ORDER : by Judge Zita L. Weinshienk regarding Pla's [181-1] motion to amend complaint [1-1] in view of results of ct ordered audit and rule 7.1

cert.,Dft shall file a response brief not to exceed 10 pgs on or before 6/8/01 (cc: all counsel) ; entry date : 5/30/01 (erv) (Entered: 05/30/2001)

05/30/2001 194 RESPONSE by Plas'to brief in support of motion in liomine regarding Parol evidence [183-1] (erv) (Entered: 06/01/2001)

06/08/2001 195 RESPONSE by defendant Laboratory Corp Amer to plas' motion to amend complaint [1-1] in view of results of ct ordered audit and rule 7.1 cert. [181-1] (pap) (Entered: 06/11/2001)

06/11/2001 196 ORDER by Judge Zita L. Weinshienk granting Pla's motion for leave to amend complaint [1-1]; Dft may file appropriate motions in response. Accordingly, it is Ordered that Pla's motion is Granted over objection. in view of results of ct ordered and rule 7.1 cert. [181-1] (cc: all counsel) ; entry date 6/12/01 (erv) (Entered: 06/12/2001)

06/11/2001 197 Fourth AMENDED COMPLAINT by plaintiff Metabolite Labs Inc; jury demand (erv) (Entered: 06/12/2001)

07/02/2001 200 Response (MOTION) by defendant Laboratory Corp Amer to dismiss Pla's 4th Amd Cmp (which is being treated as a mtn for sum jgm per 7/20/01 mo) (dlb) Modified on 07/25/2001 (Entered: 07/03/2001)

07/20/2001 201 MINUTE ORDER : by Judge Zita L. Weinshienk. Labcorp's motion under Rule 12, in response to 4th amd cmp will be treated as a motion for summary judgment. Response brief due 8/8/01, re-

ply brief due 8/22/01, setting hearing on the motion for sum jgm (to dismiss Pla's 4th Amd Cmp) [200-1] 9:30 8/29/01 (cc: all counsel) ; entry date : 7/25/01 (gms) Modified on 09/12/2001 (Entered: 07/25/2001)

08/08/2001 203 RESPONSE by plaintiff Metabolite Labs Inc, plaintiff Competitive Tech Inc to motion to dismiss Pla's 4th Amd Cmp (which is being treated as a mtn for sum jgm per 7/20/01 mo) [200-1] (erv) (Entered: 08/09/2001)

08/22/2001 204 REPLY by Dft Laboratory Corp Amer to Pla's response to motion to dismiss Pla's 4th Amd Cmp (which is being treated as a mtn for sum jgm per 7/20/01 mo) [200-1] (erv) (Entered: 08/23/2001)

09/26/2001 208 ORDER by Judge Zita L. Weinshienk denying Pla's Fourth Amended complaint [197-1], denying Dfts' Lab Corp's motion in limine to Prevent Plas' from offering Parol Evidence re: the Patent License Agreement [152-1], denying Dfts' Lab Corp's motion in limine to prevent Pla's from arguing or referring during Trial that Lab Corp infringes or willfully infringes the '658 patent [201-1] ; Trial prep conference vacated on 9/26/01 An answer shall be filed within 15 days of the 9/17/01 trial prep conf (cc: all counsel) ; entry date : 9/27/01 (erv) (Entered: 09/27/2001)

09/27/2001 209 COURTROOM MINUTES by Judge Zita L. Weinshienk denying Lab Corp's motion to dismiss Pla's 4th Amd Cmp (which is being treated as a mtn for sum jgm per 7/20/01 mo) [200-1],and deny-

ing Lab Corp's in limine to prevent Plas from arguing or referring during Trial that Labcorp infringes or willfully infringes the 658 Patent [154-1] An Answer shall be filed within 15 days of the 9/17/01 trial prep conf. Dfts', by Stipulation,shall have an Officer certify and ratify all reports submitted to Pla's pursuant to section3.02 of the License Agreement, and shall deliver to Pla's within 20 days of the 9/17/01 trial prep conf. ; entry date : 9/28/01 Court Reporter: Paul Zuckerman (erv) (Entered: 09/28/2001)

10/02/2001 211 Second Pretrial STATUS REPORT by defendant Laboratory Corp Amer (erv) (Entered: 10/03/2001)

10/02/2001 210 ANSWER by defendant Laboratory Corp Amer to 4th amended complaint [197-1]; jury demand (gms) (Entered: 10/17/2001)

10/02/2001 210 AMENDED COUNTERCLAIM [11-2] to 4th amended cmp by counter-claimant Laboratory Corp Amer (gms) (Entered: 10/17/2001)

10/02/2001 212 AMENDED ANSWER [11-1] by defendant Laboratory Corp Amer to 4th amended complaint; jury demand (gms) (Entered: 10/17/2001)

10/02/2001 212 AMENDED COUNTERCLAIM [11-2] to 4th amd cmp by counter-claimant Laboratory Corp Amer (gms) (Entered: 10/17/2001)

10/16/2001 213 REPLY TO COUNTERCLAIMS to 4th Amended Cmp [212-1] by counter-defendant Metabolite Labs Inc, counter-

defendant Competitive Tech Inc (gms) (Entered: 10/17/2001)

11/01/2001 214 TRANSCRIPT of Hrg on Motion for Sum Jgm on 10/4/01 before Honorable Zita L. Weinsheink, Judge (pages: 1-18) Prepared By: Paul Zuckerman (certified copy) (erv) (Entered: 11/02/2001)

11/05/2001 222 COURTROOM MINUTES, Jury Trial, Day 1 by Judge Zita L. Weinshienk ; jury trial held 11/5/01 , finding the motion to compel Labcorp to deliver its witheld damages information [217-1] moot ; entry date : 11/8/01 Court Reporter: Paul Zuckerman (gms) (Entered: 11/08/2001)

11/05/2001 224 EXHIBIT list by defendant Laboratory Corp Amer (erv) (Entered: 11/09/2001)

11/05/2001 225 EXHIBIT list by plaintiff Metabolite Labs Inc, plaintiff Competitive Tech Inc (erv) (Entered: 11/09/2001)

11/05/2001 226 Witness list submitted by plaintiff Metabolite Labs Inc, plaintiff Competitive Tech Inc (erv) (Entered: 11/09/2001)

11/06/2001 219 Deposition Designation (STATEMENT) by plaintiff Metabolite Labs Inc, plaintiff Competitive Tech Inc (Excerpts from Depositions) (erv) (Entered: 11/07/2001)

11/06/2001 220 BRIEF FILED by plaintiff Metabolite Labs Inc regarding the acceptance of Dr. Stabler and Dr. Allen as Experts (erv) (Entered: 11/08/2001)

11/06/2001 223 COURTROOM MINUTES, Jury Trial, Day 2 by Judge Zita L. Weinshienk ; entry date : 11/8/01 Court Reporter: Paul Zuckerman (gms) (Entered: 11/08/2001)

11/07/2001	229	COURTROOM MINUTES (Trial to Jury Day-3) by Judge Zita L. Weinshienk ; entry date : 11/9/01 Court Reporter: Paul Zuckerman (erv) (Entered: 11/09/2001)
11/08/2001	230	COURTROOM MINUTES (Trial to Jury Day 4) by Judge Zita L. Weinshienk ; entry date : 11/9/01 Court Reporter: Paul Zuckerman (erv) (Entered: 11/09/2001)
11/09/2001	232	COURTROOM MINUTES (Trial to Jury Day-5) by Judge Zita L. Weinshienk ; entry date : 11/13/01 Court Reporter: Paul Zuckerman] (erv) (Entered: 11/13/2001)
11/13/2001	231	DEPOSITION of Boger Team (Excerpts from Depositions) (erv) (Entered: 11/13/2001)
11/13/2001	234	COURTROOM MINUTES (Trial to Jury Day-6) by Judge Zita L. Weinshienk ; entry date : 11/15/01 Court Reporter: Paul Zuckerman (erv) (Entered: 11/15/2001)
11/14/2001	233	OBJECTIONS by defendant Laboratory Corp Amer and Counterdesignations to Pla's deposition Designations [231-1] (erv) (Entered: 11/14/2001)
11/14/2001	235	Proposed STATEMENT by defendant Laboratory Corp Amer of Uncontested Facts Relating to Notice (erv) (Entered: 11/16/2001)
11/14/2001	236	Proposed STATEMENT by Plas' of Uncontested Facts Relating to Notice (erv) (Entered: 11/16/2001)

11/14/2001	238	COURTROOM MINUTES (Trial to Jury Day 7) by Judge Zita L. Weinshienk ; entry date : 11/16/01 Court Reporter: Paul Zuckerman (erv) (Entered: 11/16/2001)
11/15/2001	240	COURTROOM MINUTES Trial to Jury Day-8 by Judge Zita L. Weinshienk (attached are video/reading depos re: Lai-Goldman, Andress & Novack) ; entry date : 11/20/01 Court Reporter: Paul Zuckerman (erv) Modified on 11/23/2001 (Entered: 11/20/2001)
11/16/2001	239	COURTROOM MINUTES Trial to Jury day-9 by Judge Zita L. Weinshienk. Dfts rule 50 Motion is Denied, Pla's rule 50 Motion is Denied, The Ct reserves the right to reconsider the arguments after the jury returns with a verdict ; entry date : 11/20/01 Court Reporter: Paul Zuckerman (erv) (Entered: 11/20/2001)
11/19/2001	243	COURTROOM MINUTES Trial to Jury Day 10 by Judge Zita L. Weinshienk, Jury Instructions read to the Jury ; entry date : 11/21/01 Court Reporter: Paul Zuckerman (erv) (Entered: 11/21/2001)
11/19/2001	244	Supplemental Memorandum (BRIEF) FILED by defendant Laboratory Corp Amer in support of motion for judgment as a matter of law re: minutes [239-1] (lam) (Entered: 11/23/2001)
11/20/2001	241	COURTROOM MINUTES Trial to Jury Day 11 by Judge Zita L. Weinshienk The Verdict is read into the record. It is ORDERED that the Court will not enter Jgm until 12/3/01. It is Further ORDERED that Dfts to file motions by 12/12/01; At-

tached: Stipulation and Order regarding Custody of Exhibits; Jury Instructions; Jury List; Dfts Exhibit List; Plas Exhibit List; Dfts witness list; Pla's witness list entry date : 11/21/01 Court Reporter: Paul Zuckerman (erv) (Entered: 11/21/2001)

11/20/2001 242 Special VERDICT for plaintiff against defendant; entry date : 11/21/01,The Jury finds that Dft LabCorp is not licensed under the 658 patent and that license has been terminated in whole or in part; That LabCorp has breached its license agreement by terminating it with respect to its performance of the Abbott test; Damages to the Pla Metabolite for the breach of contract in the amt of $3,652,724.61; Dft LabCorp has contributed to and induced infringement of claim 13 of the 658 patent; Damages to Pla CTI caused by the Dft LabCorp's infringement by inducment or by contributory infringement in the amt of $1,019,365.01; LabCorp has willfully infringed calim 13 of the 658 patent; claims 13 and 18 of the 658 patent are not invalid. (erv) (Entered: 11/21/2001)

11/29/2001 245 MOTIONS by defendant Laboratory Corp Amer regarding Verdict,Judgment and Rile 7.1 Compliance (erv) (Entered: 11/30/2001)

12/03/2001 246 JUDGMENT: by Honorable Zita L. Weinsheink, United States District Court Judge pursuant to [242-1] special verdict which is incorporated herein by reference as if fully set forth. Accordingly it is ORDERED that a Jgm is entered in

favor of the Plas' Metabolite Laboratories Inc., and Competitive Technologies and against Dft Laboratory Corporation of America Holdngs. It is Further ORDERED that the damages to be awarded to Pla Metabolite for Dft Lab Corp'"s bearch of contract are $3.652,724.61. It is Further ORDERED that the damages to be awarded to Pla Competitive Technologies, due Dft LabCorp's infringement by inducement or by contributory infringement are $1,019,365.01. It is Further ORDERED that post jgm interest shall accrue at the legal rate of 2.23% per annum from the date of entry of the jgm. dismissing case (cc: all counsel) ; entry date : 12/3/01 (erv) (Entered; 12/03/2001)

12/03/2001	247	Proposed Judgment and Decree (STATEMENT) by plaintiff, as requested by the Ct, and Pla's Stipulation to LabCorp's Proposed Briefing schedule re: judgment [246-2] (erv) (Entered: 12/06/2001)
12/10/2001	248	MOTION by defendant Laboratory Corp Amer to stay execution pending disposition of post trial motions (erv) (Entered: 12/10/2001)
12/12/2001	249	Renewed MOTION by defendant Laboratory Corp Amer for judgment as a matter of law (pap) (Entered: 12/13/2001)
12/12/2001	250	Memorandum (BRIEF) by defendant Laboratory Corp Amer in support of motion for judgment as a matter of law [249-1] (pap) (Entered: 12/13/2001)

12/12/2001	251	MOTION by defendant Laboratory Corp Amer for new trial (pap) (Entered: 12/13/2001)
12/12/2001	252	Memorandum (BRIEF) by defendant Laboratory Corp Amer in support of dft's alternative motion for new trial [251-1] (pap) (Entered: 12/13/2001)
12/12/2001	253	MOTION by defendant Laboratory Corp Amer to alter or amend judgment [246-2] (pap) (Entered: 12/13/2001)
12/12/2001		Proposed FINDINGS of fact and conclusions of law on patent misuse by defendant Laboratory Corp Amer (pap) (Entered: 12/13/2001)
12/12/2001	254	MOTION by plaintiff for enhanced damages , and for attorney fees for willful infringement (pap) (Entered: 12/13/2001)
12/12/2001	255	MOTION by plaintiff for permanent injunction to permanently enjoin dft from performing any homosysteine-only tests (pap) (Entered:12/13/2001)
12/12/2001	256	MOTION by plaintiff Metabolite Labs Inc for order to confirm prejudgment interest (pap) (Entered: 12/13/2001)
12/12/2001	257	MOTION by plaintiff Competitive Tech Inc for order for prejudgment interest (pap) (Entered: 12/13/2001)
12/12/2001	258	Stipulation and Opposition (RESPONSE) by plaintiff to dft's motion to stay execution pending disposition of post trial motions [248-1] (pap) (Entered: 12/13/2001)

12/19/2001	260	REPLY in Support by defendant Laboratory Corp Amer to pla's response to dft's motion to stay execution pending disposition of post trial motions [248-1] (dlb) (Entered: 12/19/2001)
01/09/2002	262	RESPONSE by Plas' Metabolite Labs Inc, Competitive Tech Inc to findings of fact and conclusions of Law on Patent Misuse [0-0], motion to alter or amend judgment [246-2] [253-1] (erv) (Entered: 01/10/2002)
01/09/2002	264	RESPONSE by defendant Laboratory Corp Amer to Plas' motion for enhanced damages [254-1] and Atty fees for willful infringement (erv) (Entered: 01/10/2002)
01/09/2002	266	RESPONSE(Opposition) by defendant Laboratory Corp Amer to Plas' motion for permanent injunction to permanently enjoin dft from performing any homosysteine-only tests [255-1] (erv) (Entered: 01/10/2002)
01/09/2002	263	RESPONSE by plaintiffs to dft's renewed motion for judgment as a matter of law [249-1], and alternative motion for new trial [251-1] (pap) (Entered: 02/28/2002)
01/09/2002	265	RESPONSE by defendant Laboratory Corp Amer to pla's motion for order for prejudgment interest [257-1], pla's motion for order to confirm prejudgment interest [256-1] (pap) (Entered: 02/28/2002)
01/11/2002	267	SUPPLEMENTAL response by defendant Laboratory Corp Amer to Plas' motions for Pre-Jgm interest containing

Treasury Bill Rate calculations [265-1] (pap) (Entered: 02/28/2002)

01/23/2002 269 REPLY by defendant Laboratory Corp Amer to Pla's response to Dfts motion to alter or amend judgment [246-2] [253-1] (erv) (Entered: 01/23/2002)

01/23/2002 272 REPLY Brief by plaintiff Metabolite Labs Inc to motion for permanent injunction to permanently enjoin dft from performing any homosysteine only tests [255-1] (erv) (Entered: 01/24/2002)

01/23/2002 273 REPLY by plaintiff Metabolite Labs Inc to Dfts response to Pla's motion for enhanced damages [254-1] and Atty Fees for Labcorp's willful infringement (erv) (Entered: 01/24/2002)

01/23/2002 268 REPLY in support by defendant Laboratory Corp Amer of its renewed motion for judgment as a matter of law [249-1], motion for new trial [251-1] (pap) (Entered: 02/28/2002)

01/23/2002 271 REPLY by plaintiff Competitive Tech Inc concerning motion for order for prejudgment interest [257-1] (pap) (Entered: 02/28/2002)

01/24/2002 270 REPLY by plaintiff Metabolite Labs Inc to dft's response to Pla's motion for order to confirm prejudgment interest [256-1] (pap) (Entered: 02/28/2002)

02/11/2002 274 MOTION by defendant Laboratory Corp Amer for leave to file corrected Memorandum in Support of Laboratory Corporation of America Holding's Renewed Motion for Jgm as a matter of Law (erv) (Entered: 02/11/2002)

02/11/2002		Tendered Corrected Memorandum submitted by defendant Laboratory Corp Amer re: motion for leave to file corrected Memorandum in Support of Laboratory Corporation of America Holding's Renewed Motion for Jgm as a matter of Law [274-1] (erv) (Entered: 02/11/2002)
05/13/2002	275	MOTION by defendant (for order) to take judicial notice in support of renewed motion for judgment as a matter of law and in opposition to plas' motion for permanent injunction and rule 7.1 certification (pap) (Entered: 05/14/2002)
05/30/2002	276	Opposition (RESPONSE) by plaintiffs to dft's motion (for order) to take judicial notice in support of renewed motion for judgment as a matter of law and in opposition to plas' motion for permanent injunction [275-1] (pap) (Entered: 05/31/2002)
06/14/2002	277	REPLY by defendant Laboratory Corp Amer in support of motion (for order) to take judicial notice in support of renewed motion for judgment as a matter of law and in opposition to plas' motion for permanent injunction [275-1] (pap) (Entered: 06/17/2002)
11/20/2002	278	ORDER by Judge Zita L. Weinshienk: granting dft's motion for leave to file corrected memorandum in support of Laboratory Corporation of America Holding's renewed motion for jgm as a matter of law [274-1]; denying dft's motion for judgment as a matter of law [249-1]; denying dft's alternative motion for new trial [251-1]; denying dft's motion to alter or amend judgment [246-2],

[253-1]; denying dft's motion to take judicial notice in support of renewed motion for judgment as a matter of law and in opposition to plas' motion for permanent injunction [275-1]; granting plas' motion for enhanced damages and atty fees for willful infringement as to the enhanced damages to pla CTI in the amt of $1,019,365.01 and will be considered as to atty fees upon submission of an affidavit from csl [254-1], [254-2]; granting plas' motion for permanent injunction [255-1]; granting pla Metabolite Laboratories, Inc's motion to confirm prejudgment interest in the amt of $473,946.97 [256-1]; granting pla Competitive Technologies, Inc's motion for prejudgment interest in the amt of $132,264.27 [257-1]; finding dft's motion to stay execution pending disposition of post trial motions [248-1] denied as moot; and judgment will be amended to reflect the addl amounts above (cc: all counsel) ; entry date .: 11/20/02 (lam) (Entered: 11/20/2002)

11/20/2002 279 AMENDED JUDGMENT by Judge Zita L. Weinshienk: that judgment is entered in favor of plas Metabolite Laboratories, Inc. and Competitive Technologies and against dft Laboratory Corporation of America Holdings; that damages are awarded to pla Metabolite for dft LabCorp's breach of contract in the amt of $3,652,724.61; that damages are awarded to pla Competitive Technologies, Inc., due to dft LabCorp's infringement by inducement or by contributory infringement in the amt of

		$1,019,365.01; that pla Metabolite Laboratories, Inc. is awarded $437,946.97 in prejudgment interest; that pla Competitive Technologies,Inc. is awarded $132,264.27 in prejudgment interest; and post- judgment interest shall accrue at the legal rate of 2.23% per annum from the date of entry of judgment re: [278-1] order, [246-2] judgment, [242-1] verdict (cc: all counsel) ; entry date : 11/20/02 (lam) (Entered: 11/20/2002)
11/20/2002	280	Corrected (AMENDED) memorandum of law by defendant Laboratory Corp Amer in support of renewed motion for judgment as a matter of law [249-1] (lam) (Entered: 11/21/2002)
11/22/2002	281	Unopposed MOTION by defendant Laboratory Corp Amer for (order) suspension of permanent injunction through 11/26/02 and certificate of compliance with LR 7.1 (pap) (Entered: 11/26/2002)
11/26/2002	282	Emergency MOTION by defendant Laboratory Corp Amer for stay pending appeal, suspension of permanent injunction , and for (order) approval of supersedeas bond or other security and certificate of compliance with LR 7.1 (pap) Modified on 11/27/2002 (Entered: 11/27/2002)
11/26/2002	283	Opposition by plaintiffs to Labcorp's motion for stay pending appeal suspension of permanent injunction [282-1], motion for (order) approval of supersedeas bond or other security [282-2] (pap) Modified on 11/27/2002 (Entered: 11/27/2002)

11/26/2002	285	MOTION by defendant Laboratory Corp Amer for forthwith (to expedite) consideration of its emergency motion for stay pending appeal, suspension of permanent injunction and for approval of supersedeas bond or other security (pap) (Entered: 11/27/2002)
11/26/2002	286	ORDER by Judge Zita L. Weinshienk granting motion for (order) suspension of permanent injunction through 11/26/02 [281-1] (cc: all counsel) ; entry date : 11/27/02 (pap) (Entered: 11/27/2002)
11/26/2002	293	COURTROOM MINUTES by Judge Zita L. Weinshienk regarding [282-1] motion for stay pending appeal, suspension of permanent injunction; hearing continued until 11/27/02; Suppersedeas Bond for $6,578,527.00 approved; Stay is continued until further order of the Court ; entry date : 12/4/02 Court Reporter: Gwen Daniel (pap) (Entered: 12/04/2002)
11/27/2002	287	TRANSCRIPT of Further proceedings on 11/26/02 before Senior Judge Weinshienk (pages: 1-38) Prepared By: Gwen Daniel (certified copy) (pap) (Entered: 11/29/2002)
11/27/2002	288	NOTICE OF APPEAL TO FEDERAL CIRCUIT by defendant/counter-claimant Laboratory Corp Amer, re: judgment amend dated 11/20/02 [279-1], order [278-1] dated 11/20/02 and order dated 11/19/00 [118-1] ; Trancscript Purchase Order Form due 12/9/02 ; Notice mailed to all counscl on 11/29/02 Fee Status: $100 and $5 fee not paid (msn) Modified on 12/03/2002 (Entered: 11/29/2002)

11/27/2002	289	COURTROOM MINUTES by Judge Zita L. Weinshienk granting motion for stay pending appeal, suspension of permanent injunction [282-1] ; 6% royalties shall be paid on all future testing as to CTI until the ruling of the Federal Circuit; 21.5% royalties shall be paid on all future testing as to Metabolite; 6% royalties shall be paid on half the tests performed since the judgment in this case as to CTI; entry date : 11/29/02 Court Reporter: Gwen Daniel (pap) (Entered: 11/29/2002)
12/02/2002	290	$100.00 fee and $5.00 fee paid. Receipt No 239671. Court of Appeals Notified. appeal [288-1] (msn) (Entered: 12/02/2002)
12/02/2002	292	TRANSCRIPT of further proceedings on 11/27/02 before Judge Weinshienk (pages: 41) Prepared By: Gwen Daniel (certified copy)
12/05/2002	295	ORDER by Judge Zita L. Weinshienk granting motion for stay pending appeal, granting suspension of permanent injunction [282-1] with conditions, granting motion for (order) approval of supersedeas bond or other security [282-2] in the amount of $6,578,527.00 to be posted within days; denying as moot motion for forthwith (to expedite) consideration of its emergency motion for stay pending appeal, suspension of permanent injunction and for approval of supersedeas bond or other security [285-1] (cc: all counsel) ; entry date : 12/5/02 (pap) (Entered: 12/05/2002)

12/31/2002	305	REPORTER'S TRANSCRIPT of Trial to Jury on 11/05/01, Volume I, before Judge Weinshienk (Re: [288-1]) Pgs 1-185 Cert Copy Prepared By: Paul Zuckerman (msn) Modified on 01/02/2003 (Entered: 01/02/2003)
12/31/2002	306	REPORTER'S TRANSCRIPT of Trial to Jury on 11/6/01, Volume II, before Judge Weinshienk (Re: [288-1]) Pgs 186-389 Cert Copy Prepared By: Paul Zuckerman (msn) Modified on 01/02/2003 (Entered: 01/02/2003)
12/31/2002	307	REPORTER'S TRANSCRIPT of Trial to Jury on 11/7/01, Volume III, before Judge Weinshienk (Re: [288-1]) Pgs 390-593 Cert Copy Prepared By: Paul Zuckerman (msn) Modified on 01/02/2003 (Entered: 01/02/2003)
12/31/2002	308	REPORTER'S TRANSCRIPT of Trial to Jury on 11/8/01, Volume IV, before Judge Weinshienk (Re: [288-1]) Pgs 594-787 Cert Copy Prepared By: Paul Zuckerman (msn) Modified on 01/02/2003 (Entered: 01/02/2003)
12/31/2002	309	REPORTER'S TRANSCRIPT of Trial to Jury on 11/9/01, Volume V, before Judge Weinshienk (Re: [288-1]) Pgs 788-994 Cert Copy Prepared By: Paul Zuckerman (msn) Modified on 01/02/2003 (Entered:01/02/2003)
12/31/2002	310	REPORTER'S TRANSCRIPT of Trial to Jury on 11/13/01, Volume VI, before Judge Weinshienk (Re: [288-1]) Pgs 995-1200 Cert Copy Prepared By: Paul Zuckerman (msn) (Entered: 01/02/2003)

12/31/2002	311	REPORTER'S TRANSCRIPT of Trial to Jury on 11/14/01, Volume VII, before Judge Weinshienk (Re: [288-1]) Pgs 1201-1375 Cert Copy Prepared By: Paul Zuckerman (msn) (Entered: 01/02/2003)
12/31/2002	312	REPORTER'S TRANSCRIPT of Trial to Jury on 11/15/01, Volume VIII, before Judge Weinshienk (Re: [288-1]) Pgs 1376-1589 Cert Copy Prepared By: Paul Zuckerman (msn) (Entered: 01/02/2003)
12/31/2002	313	REPORTER'S TRANSCRIPT of Trial to Jury on 11/16/01, Volume IX, before Judge Weinshienk (Re: [288-1]) Pgs 1590-1733 Cert Copy Prepared By: Paul Zuckerman (msn) (Entered: 01/02/2003)
12/31/2002	314	REPORTER'S TRANSCRIPT of Trial to Jury on 11/19/01, Volume X, before Judge Weinshienk (Re: [288-1]) Pgs 1734-1857 Cert Copy Prepared By: Paul Zuckerman (msn) (Entered: 01/02/2003)
12/31/2002	315	REPORTER'S TRANSCRIPT of Trial to Jury on 11/20/01, Volume XI, before Judge Weinshienk (Re: [288-1]) Pgs 1858-1879 Cert Copy Prepared By: Paul Zuckerman (msn) (Entered: 01/02/2003)
01/13/2003	318	ORDER staying permanent injunction pending appeal by Judge Zita L. Weinshienk regarding [278-1] order (modifies orders entered at oral argument on 11/27/02) (cc: all counsel) ; entry date : 1/14/03 (pap) (Entered: 01/14/2003)
08/05/2003	334	Order and JUDGMENT re: Attorney Fees and Costs: by granting plas' motion for attorney fees for willful infringement [254-2], granting plas' motion for attorney fees [294-1] to the extent that plas

		CTI and Metabolite will be awarded $1,105,605.07 in reasonable attorney fees; denying dft's motion for order compelling plas to produce documentation reflecting allocation of payment of fees by and between Metabolite and CTI [316-1]; Granting plas' motion to review clerk's taxation of costs and dft will be taxed an additional $6,993 in costs, for a total of $25,906 (cc: all counsel) ; entry date : 8/5/03 (pap) (Entered: 08/05/2003)
09/03/2003		$100.00 fee and $5.00 fee paid. Receipt No 246012. re: appeal [335-1] (msn) (Entered: 09/04/2003)
09/03/2003	335	NOTICE OF APPEAL to the U.S. COURT OF APPEALS FOR THE FEDERAL CIRCUIT by Laboratory Corp Amer re: judgment filed 8/5/03 [334-1] and from all other orders incorporated by reference in or related in any way to the Court's 8/5/03 "Order and Judgment Re Attorney Fees and Costs," other than those orders that are already on appeal pursuant to the Notice of Appeal filed in this case on 11/27/03; Notice of transcript purchase order form due 9/15/03; Notice mailed to all counsel on 9/4/03 (msn) Modified on 09/04/2003 (Entered: 09/04/2003)
08/16/2004	342	MANDATE from the Federal Circuit Court of Appeals; CA # 03-1120; Dt issued 8/12/04; Judgment of 6/8/04 affirming the decision of the District Court on appeal [288-1] (djs) (Entered: 08/16/2004)
05/17/2005	395	JOINT MOTION to Stay Case until 7/5/05 pending the Supreme Court ruling

by Plaintiffs Metabolite Laboratories, Inc., Competitive Technologies, Inc., Defendant Laboratory Corporation of America Holdings. (pap,) (Entered: 05/18/2005)

05/18/2005 396 MINUTE ORDER granting [395] Joint Motion to Stay. Case is stayed until 7/5/05. Hearing set 5/19/05 is vacated. Joint status report due on or before 7/8/05. Entered by Judge Zita L. Weinshienk on 5/18/05. (pap,) (Entered: 05/19/2005)

07/18/2005 398 MINUTE ORDER re: [396] Order on Motion to Stay. Status Report due by 10/17/2005.Entered by Judge Zita L. Weinshienk on 7/18/05. (pap,) (Entered: 07/18/2005)

10/14/2005 399 MINUTE ORDER: the stay entered by the court on 5/18/05 is extended to 10/18/05. Status Report due by 10/18/2005 by Judge Zita L. Weinshienk on 10/14/05. (dlb,) (Entered: 10/14/2005)

10/24/2005 402 MINUTE ORDER Stay enter by 399 Order shall remain in effect until November 10, 2005. Joint Status Report due by 11/10/2005.Entered by Judge Zita L. Weinshienk on 10/24/05. (pap,) (Entered: 10/24/2005)

11/15/2005 404 MINUTE ORDER, It is ORDERED that the stay entered by the Court in the Minute Order filed on October 24, 2005, shall remain in effect until the U.S. Supreme Court issues a ruling on the issue described in the parties' November 10, 2005, Joint Status Report, absent further

order. Set Deadlines: Status Report due by 6/30/2006. by Judge Zita L. Weinshienk on 11/15/05. (erv,) (Entered: 11/15/2005)

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLORADO

Civil Action No. 99-Z-870

METABOLITE LABORATORIES, INC., *et al.*,

Plaintiffs,

vs.

LABORATORY CORPORATION OF AMERICA HOLDINGS,

Defendant.

REPORTER'S TRANSCRIPT
(Markman Hearing)

Proceedings before the HONORABLE ZITA L. WEINSHIENK, Judge, United States District Court for the District of Colorado, commencing at 10:18 a.m., on the 16th day of November, 2000, in Courtroom C-400, United States Courthouse, Denver, Colorado.

* * * *

[Page 6, line 22 to Page 9, line 13]

THE COURT: The word "correlating": From the claim language and the prosecution history, it must be a verb, not a noun; and that means to establish a mutual or reciprocal relationship between.

Let's see. "Deficiency." Did I cover that? Deficiency means—and this is based on the claim language and corroborated by the patent record. "Deficiency" means shortage of a substance necessary to health.

And it appears to me it does not and should not have the addition of words talking about hematologic or neuropsychiatric abnormalities.

So we've got detecting, deficiency, elevated, correlating. "Distinguishing" really comes in with Claim 18. If you want, we can talk about that. But I don't think it's probably necessary. It seems to me that it's pretty clear that it just means to separate into kinds, classes, or categories. And I don't think the parties are in dispute about that.

The problem arises with the word correlating. And we know from reading this brief and from reading the history and the fact that the Claim 13 was denied and then amended and the inventor was told to put in the steps—I'm trying to remember the language. Let me just get that.

Claim 13 was rejected because the homocysteine tests alone were already known in prior history and the inventor was told actually to put in—I think the language was discrete tests—steps. I don't have that right in front of me now, but we'll find it.

We know from case law going all the way back—

Okay. Here it is: "Patent examiner required a method involving discrete, sequential process steps." We know from that that "correlation" must be a verb and not a noun. It has to be an active step, because the assaying step is not sufficient. It's a statement.

But we know going all the way back in history, early cases, that an invention is not just an idea, it is not just a mental discovery. It must combine the idea with the means of putting it into practice and producing a desired result.

And so until the discovery is put into a practical form, there is no invention. There is no valid patent.

Let's see. The Supreme Court, way back when, in the *Symington* case said, "A conception of the mind, not represented in some physical form, is not an invention."

So if one takes the statement, which may very well be a wonderful new conception, that if there is an elevated level of total homocysteine and if that elevated level is correlated in body fluid with deficiency—can be correlated—that elevated level can be correlated in said body fluid with deficiency of cobalamin or folate, that is certainly a new idea, something original.

But what is the practicable—practical form of that? What are the actual steps? What are the discrete, sequential steps for putting into practice this new statement?

And I really have problems with that, quite frankly. And I'm not sure that that's a subject for today's hearing, which is a *Markman* hearing. But it certainly is something that we're going to have to talk about, because as wonderful as this thought is, unless there is some step, practicable step, and it's put into a practical form, then we don't have an invention. Statements are wonderful, but they're not inventions unless they're put into some sort of physical form or practical form.

And that's what I think the patent examiner was requiring. And I'm not quite sure how Claim 13 actually in the last state was approved, unless there is something that I'm not understanding—and I'm certainly not a scientist, as Dr. Allen is—as to how this statement, ingenious as it may be, can be put into a practical form.

* * * *

[Page 13, line 16 to Page 15, line 12]

MR. BEATON: Maybe I should focus on this word "correlating," which I think has troubled you with respect to what happened in the prosecution history. I think that has gotten a bit confused here.

As I read the prosecution history, the professors initially submitted Claim 13, stating that it was a method to detect a deficiency in cobalamin or folate by assaying for an elevated level of total homocysteine.

THE COURT: Okay.

MR. BEATON: So this idea of there being some sort of tie between the assay for elevated total homocysteine and a deficiency in folate or cobalamin was there right from the get-go.

Now, what the examiner came back and said was, I'm not so sure that you've really set this forth in discrete steps.

THE COURT: Exactly.

MR. BEATON: So the professors came back and said, Okay, let's take a step-by-step approach to this just to be clear. We've always said all along that there has to be something to do with deficiencies in vitamins. The claim did not cover, as it was initially filed, all total homocysteine tests. Never covered that. It doesn't cover that now. We don't so contend. There has to be this second step of correlating an elevated level of total homocysteine—excuse me—with deficiencies of at least one of the two vitamins.

THE COURT: And let me just interject. It appears to me that that step is covered in Claim 18.

MR. BEATON: Yes. Claim 18 goes a little bit further. It says: Not only will you correlate an elevated level of total homocysteine with deficiencies in the two vitamins, you'll figure out which of the two is deficient—

THE COURT: Right.

MR. BEATON: —by a separate assay for methylmalonic acid, MMA.

But in Claim 13, you don't have to figure out which of the two is deficient; you just have to assay for elevated levels of total homocysteine, which LabCorp has admitted that it does. And then the second step, which is the one in dispute, you have to correlate an elevated level of total homocysteine with a deficiency of cobalamin or folate. You don't have to say

which one. You just have to say at least one of them is deficient.

That's the step that was specifically added by the professors. That step is required.

THE COURT: And how do you put into practical application that second step? Because that's what's not clear to me or not clear from a reading of Claim 13.

* * * *

[Page 16, line 19 to Page 23, line 19]

THE COURT: Well, let me just ask you, because I'm not sure I'm understanding, and I do want to understand: Are you suggesting another step to 13?

MR. BEATON: No. There are two steps. There has to be an assay, which of course, is an affirmative act. That's more than an idea.

THE COURT: Okay. High homocysteine.

MR. BEATON: And there has to be a second step. Now, a person who just does an assay somehow armed with the knowledge—and this goes to your idea point, I think—that there is some sort of correlation between elevated homocysteine and deficiencies in the vitamin—that person may or may not infringe the patents. We don't need to answer that, because that's not this defendant.

There needs to be a second step. There needs to be this correlating. And that is done by this defendant, and he so admits with respect to the panel test; that the correlating as I mentioned constitutes the act of presenting the test results together with information showing this mutual or causal or parallel relationship, which is the definition of "correlate."

We got into this because we started on the question of extrinsic evidence, and I think that that extrinsic evidence of the defendant's specific admissions that they do correlate in

the panel test answers your question as to what in the real world does correlating look like.

THE COURT: And are you—is the plaintiff objecting to the—what appears to be really a plain meaning, a meaning derived from the language of the claim that "correlating" means to establish a mutual or reciprocal relationship?

MR. BEATON: No. We would agree that that is precisely the definition of correlating.

THE COURT: Okay.

MR. BEATON: And specifically, it does not require some sort of perfection, it does not require a medical diagnosis, it doesn't require a certain determination.

THE COURT: Does it require a practical form of ascertaining, of correlating?

MR. BEATON: I believe it requires something more than knowledge upstairs in the mind of somebody. It requires taking that homocysteine level that has been determined by an assay and comparing it against some sort of benchmark so that a person can make a judgment as to whether it's elevated to the point that there is a likelihood, not a certainty, but a likelihood of one of the two vitamin deficiencies.

If this case were—

THE COURT: Comparing it in somebody's mind, or comparing it with a practical test?

MR. BEATON: I think that there has to—there has to be more than just a mental step in someone's mind.

THE COURT: Right.

MR. BEATON: There needs to be—in my mind, at least—there needs to be something presented that shows this parallel, mutual, or reciprocal, or causal—whatever you want to call it—this relationship. Something needs to be presented showing that relationship.

THE COURT: I see that in Claim 18, but I don't in Claim 13. So where is it in Claim 13?

MR. BEATON: I believe it's in the word "correlating," and I believe that the patent office was fairly explicit in saying we want that set forth in a discrete sort of way.

THE COURT: Maybe you could just tell me, not a scientist, but tell me what practical steps are done to do that? Because we know from the case law that there must be a practical form. Can't be just a mental conception.

So what do you do? No. 1, No. 2, No. 3, No. 4. What do you do to correlate?

MR. BEATON: To answer that, maybe we should look at their directory of services which their patent attorney stated two years ago contains the correlating step in, and their Rule 30(b)(6) witness acknowledged the same in his deposition last winter. It's in Exhibit C to our opening Markman brief.

THE COURT: Well, who are you talking about, "they"? We're talking about plaintiff. Plaintiff is the one that has Claim 13. Every person—if Claim 13 is properly patented, it has two steps for every scientist, every person who uses it. Every person using this invention or method or practical invention uses it in the same way. How do they use it, using the word "correlating"? That's the problem I have with it.

I think it's hard for you to tell me that.

MR. BEATON: Well, the answer to the question is what—the answer to the question of what constitutes the correlate step, I think, is given by example in the LabCorp directory of services.

THE COURT: No, I don't think you can go to LabCorp.

I'm talking about the plaintiff, the patent. We can't look at what LabCorp does. You have to look at what the patent, what Claim 13 says.

MR. BEATON: Okay. You're interested in an example of the correlation occurring in the description of the patent?

THE COURT: No, I'm not interested in an example. I'm interested in what Claim 13 says you do.

MR. BEATON: Well, Claim 13 says you correlate your elevated homocysteine with a deficiency in one of the two vitamins.

THE COURT: Okay. And I want to know what the practical steps are for doing that.

MR. BEATON: Okay. First step is to assay for total homocysteine.

THE COURT: Well, we've done that. The first step, I don't have problems with.

MR. BEATON: Right. That results in a number.

The person takes that number and compares it against some sort of benchmark that he has. If it's above that benchmark, then he has some evidence that the total homocysteine is elevated. The patent teaches that that can be interpreted to mean that there is a deficiency in one of the two vitamins. And the data in the patent support that.

Now, if the person doesn't do that comparison—maybe this is what you're looking for, your Honor. The person needs to do a comparison. The person needs to compare the homocysteine result against a benchmark; and if it's elevated, then it correlates with a deficiency in the vitamins. If it's not elevated against that benchmark, then it doesn't.

Now, as you pointed out, the benchmark—

THE COURT: Well, I'm happy—that's the first step you're talking about. I'm asking you about the second step. The correlation. Because, indeed, it seems to me that has to be a step, it has to be a practical step, much as the first step, which is measuring the homocysteine to see if it's elevated.

MR. BEATON: I think you may be looking for a mechanical sort of step, where, for example, in the first step the laboratory does an assay.

There is no mechanical step here, and there need not be for the claim to be patentable. The step here indeed is a comparison step. That's perfectly fine under patent law. We don't need for there to be something like the homocysteine is mixed up with this or that and it turns blue.

THE COURT: Okay. What is the comparison?

MR. BEATON: The comparison is taking that homocysteine level determined by the first step and comparing it against some benchmark to determine whether it's elevated and hence correlates with vitamin deficiencies.

THE COURT: Hold on. Comparing it to see if it's elevated is the first step. I'm interested in the second step, because there has to be a second step, or at least I think there does because that's what the patent examiner said. There has to be discrete, sequential process steps.

I have no problem with whatever you do to find out you've got a homocysteine which is at an elevated level. And I think "elevated" pretty much means what we agreed on above the normal range, whether it's the normal range for a human or for an animal. And that can be determined.

But what is the second step? If you can just explain that to me so I can try to understand it, fine. Maybe this is something that only a scientist can understand, so tell me if that's the case.

MR. BEATON: Well, let me take another shot.

I think the second step is taking that homocysteine level that's been determined by the first step, comparing it against a benchmark chosen by the tester, which need not be 22 or any other particular benchmark but some benchmark and saying, aha, it's above that benchmark. Based on our data, which may be presented in a table, it may be presented in a

computer program, it may be presented in a variety of different ways, there is a likelihood—and here's the step—there is a likelihood of a vitamin deficiency, or conversely, there is not a likelihood of a vitamin deficiency.

THE COURT: Well, wasn't that the wording of Claim 13 before it was revoked or rejected and then amended?

MR. BEATON: I think it was close to that. But what it didn't do was set forth this correlating in a distinct step in the body of the claim. Instead, it was in the preamble of the claim. It read "A method for detecting a deficiency of cobalamin or folate in warm blooded animals by assaying a body fluid for an elevated level of total homocysteine."

The examiner said, Well, okay, you assay for an elevated level of total homocysteine, but what do you do with that—said the examiner.

The professors said well, we told you in the preamble what you do with that; but if you want us to put that in a distinct step in the body, fine. What you do is you take that total homocysteine level that you assayed for and you compare it with the benchmark to reach a determination, or a likelihood.

* * * *

[Page 29, line 1 to Page 31, line 4]

THE COURT: Okay. I understand what you're saying.

So what is it? Let's be very specific what you're saying, then, about that. You're talking about the second step, the correlation step.

MR. HIGGINS: Correct your Honor. The second step.

As that claim is written and in view of the prosecution history and specification, the correlating step requires a person to show that the elevated level of total homocysteine was caused by a deficiency of cobalamin or folate for that particular assay. That is the only way that claim can stake out a boundary where the—

THE COURT: Well, I don't see the words "caused by" in the patent.

MR. HIGGINS: Your Honor, the language, the interpretation of correlating, it says, "correlating is to establish a mutual or reciprocal relationship between."

THE COURT: Yes. Yes.

MR. HIGGINS: You think the step of correlating an elevated level with a deficiency—in other words, to correlate, you show or establish that the elevated level results are caused by the deficiency.

It says, "to show or establish," or you used the term "to establish" a mutual or reciprocal relationship between.

And without taking some active step to make that correlation or determination, then just an elevated level of total homocysteine falls within Claim 13, because based on the claim interpretation that Mr. Beaton and the plaintiffs have tried to present under claim interpretation, again, how does one know what assays for total homocysteine fall within Claim 13 and those that don't? Those prior art assays that were specifically noted by the examiner—

THE COURT: Well, if—it seems to me that the plain meaning of Claim 13 is that if you have this elevated level of homocysteine—in other words, above the normal range—and it depends, I guess, on which fluid you are testing and maybe which animal. I'm not as sure as you are that this is humans only, but perhaps it is.

MR. HIGGINS: No, your Honor, the claim does cover animals. But as far as the lawsuit goes—

THE COURT: Have you stipulated humans only?

MR. HIGGINS: LabCorp mainly does for humans.

THE COURT: Okay. So above the normal range. And it indicates that there might be this deficiency, and so you're

saying—you're saying that you have problems in seeing what the second step is or the active step.

MR. HIGGINS: That's correct, your Honor. Just indicating is not a step; it's not an active step.

Your Honor, for some extrinsic evidence from the—

THE COURT: You guys are the experts on patents. Can you patent a brilliant idea?

MR. HIGGINS: No, your Honor, you cannot patent an idea.

THE COURT: Because this may be a brilliant idea, and the question is: Is it patentable?

* * * *

[Page 34, line 24 to Page 35, line 14]

MR. HIGGINS: Again, for correlating, I don't know that we disagree with the Court's statement that correlating means to establish a mutual or reciprocal relationship between.

THE COURT: Okay.

MR. HIGGINS: But what does that mean? When we get to trial, the jury has the task of taking the claim as it's been construed and applying it to the conduct.

And so what does it mean to establish a mutual or reciprocal relationship between an elevated level of total homocysteine and a deficient—

THE COURT: You're assuming that this issue is going to get to the jury. I've indicated that I have problems with it as a matter of law. If, indeed, I'm not convinced that it meets the legal test of being a combination of an idea and a means of putting it into practice, it's never going to get to the jury.

* * * *

[Page 50, lines 4-19]

THE COURT: Now, if you show the homocysteine level that was determined by the assay in relation to that range and you explain the relationship between elevated homocysteine and the vitamin deficiencies, you have thereby performed a correlating of the two.

Again, it's probably an issue for another day.

THE COURT: Again, is that a mental step, or is that an actual, practical, physical step which is required for a valid patent?

MR. BEATON: Well, in the case of LabCorp, they actually do this in a physical way. They do present tables showing ranges and probabilities, and so on.

Now, whether a physician who does this in his office merely with the knowledge of the relationship upstairs in his mind would infringe the patent I think is another question that's not going to be in this case.

* * * *

[Page 59, line 18 to Page 60, line 2]

MR. JABLONSKI: I do think having heard the argument here today that you have identified in your opening comments precisely what the question is in this Step 2, and that is what is correlating. And you've said that that requires an active step.

And while Mr. Beaton has attempted to verbalize some active step, what he's really describing is simply the general knowledge. There is no active step done by LabCorp, and that's why there is no infringement here. And he has struggled mightily to respond to your question, but there is no response. That's the bottom line here.

* * * *

[Filed Nov. 29, 2000]

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLORADO

Civil Action No. 99-Z-870

METABOLITE LABORATORIES, INC.,
a Colorado corporation, and
COMPETITIVE TECHNOLOGIFS, INC.,
a Delaware corporation,

Plaintiffs,

v.

LABORATORY CORPORATION OF AMERICA
HOLDINGS d/b/a LABCORP,
a Delaware corporation,

Defendant.

ORDER

This matter was before the Court on November 15, 2000, for oral argument on the construction of terms in plaintiffs' U.S. Patent No. 4,940,658, specifically Claim 13. Claim 13 reads:

> A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> > assaying a body fluid for an elevated level of total homocysteine; and correlating an elevated level of total homocysteine in said body fluid with deficiency of cobalamin or folate.

(defendant's exhibit A, column 41, lines 58-65).

"[T]he court has the power and obligation to construe as a matter of law the meaning of language used in the patent

claim." *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). The court may not rely upon extrinsic evidence to construe a claim unless terms remain ambiguous after consideration of the intrinsic evidence, which includes the claim terms, the patent specification, and the prosecution history. *Vitrionics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996). If the claim language is clear on its face, consideration of the rest of the intrinsic evidence "is restricted to determining if a deviation from the clear language of the claim is justified." *Interactive Gift Express, Inc. v. Compuserve Incorp.*, 2000 WL 1644598 (Fed. Cir.) (November 3, 2000). This Court has relied on the prosecution history to construe a term where the patentee relinquished a potential claim construction in an amendment to the claim or in an argument to overcome or distinguish a reference. *Elkay Mfg. Co. v. Ebco Mfg. Co.*, 192 F.3d 973, 979 (Fed. Cir. 1999).

The Court will construe the following terms: "detecting," "deficiency," "elevated," and "correlating." Based on the claim language, the word "detecting" is means "determining the existence of." In the context of the patent specification, the term does not mean that a deficiency in cobalamin or folate must be determined with 100% accuracy, however.

The word "deficiency" means "a shortage of a substance necessary to health." Although defendant argues that a physician logically would not perform the assay unless alerted to the possibility of a deficiency by some symptom, to construe the term to include a reference to a hematologic or neuropsychiatric abnormality would be improper. It would import a limitation from the specification that is not justified by the claim language or patent record. Throughout most of the patent specification, "deficiency" is used to denote a shortage of a necessary substance.

"Elevated" means "raised above the normal range." Construing the term to refer to a specific numeric range would not be consistent with the claim language. The normal range

depends both upon which body fluids are measured, and which animal is tested. The prosecution history indicates the patent examiner initially rejected Claim 13 because the applicant failed to include "quantitative language." (defendants' exhibit F, p. 3). However, the patent examiner was satisfied with the applicant's reference to the normal ranges for homocysteine in serum and urine at the time of the invention as described in the patent specification and with the applicant's explanation that "methods for determining such ranges are well-known in the art." (defendant's exhibit G, pp. 7-8).

The prosecution history indicates that the term "correlating" must be one of several "discrete, sequential process steps" and "[t]he final step should be clearly related to the preamble of the claim." (defendant's exhibit F, p. 3). The patent examiner initially rejected Claim 13 because it appeared to patent a simple homocysteine test, which is known in prior art, and the preamble did nothing more than suggest an intended use for the homocysteine test. (defendant's exhibit H, p. 2). Therefore, the term is construed as meaning "to establish a mutual or reciprocal relationship between." "Correlating" is a verb, and must mean more than the simple existence of a relationship between a high level of homocysteine and a deficiency in cobalamin or folate. It must comprise a discrete, sequential process step, as suggested by the patent examiner.

The Court rejects defendant's argument that "correlating" is limited by the language of Claim 13 to correlation with hematologic or neuropsychiatric symptoms in order to confirm a deficiency in cobalamin or folate. Defendant's definition is derived from a non-limiting example, (defendant's exhibit A, column 10, line 25 - column 12, line 7), that described a study done by applicant Dr. Robert Allen in which the homocysteine test was used to confirm cobalamin folate deficiencies in patients displaying hematologic or neuropsychiatric symptoms. The study was included in the patent specification as an example of one potential use of the

applicant's discovery. Defendant's construction would read a limitation into the claim that would not be consistent with the term "correlating" as it is used throughout the patent specification.

The terms "detecting," "deficiency" and "elevated" in Claim 18 are construed as they are in Claim 13. Accordingly, it is

ORDERED that the term "detecting" in Claim 13 is construed to mean "determining the existence of." It is

FURTHER ORDERED that the term "deficiency" in Claim 13 is construed to mean "a shortage of a substance necessary to health." It is

FURTHER ORDERED that the term "elevated" in Claim 13 is construed to mean "raised above the normal range." It is

FURTHER ORDERED that the term "correlating" in Claim 13 is a verb that is construed to mean "to establish a mutual or reciprocal relationship between," and that describes a discrete step in a sequential process.

DATED at Denver, Colorado, this 29 of November, 2000.

BY THE COURT:

/s/ Zita L. Weinshienk
ZITA L. WEINSHIENK, Senior Judge
United States District Court

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLORADO

Civil Action No. 99-Z-870

METABOLITE LABORATORIES, INC., *et al.*,

Plaintiffs,

vs.

LABORATORY CORPORATION
OF AMERICA HOLDINGS,

Defendant.

REPORTER'S TRANSCRIPT
(Hearing on Motions for Summary Judgment)

Proceedings before the HONORABLE ZITA L. WEINSHIENK, Judge, United States District Court for the District of Colorado, commencing at 9:20 a.m., on the 1st day of March, 2001, in Courtroom C-400, United States Courthouse, Denver, Colorado.

* * * *

[Page 10, lines 3-21]

THE COURT: You know, we've talked about this before. The claim has to describe an invention in a way that allows people who read it to understand the scope. It has to do something. I think we've gone over this before. That's the problem. There has to be notice or an explanation to people. And you're saying it's there.

MR. BEATON: I am saying it's there. If I may, I can point you to the place in the—places in the patent specification that describe this step. I have—

THE COURT: Well, Claim 13, it would appear to me—and I could be wrong; I'm not a scientist, certainly—does not describe a correlating step except for what we've talked about, this mental understanding that there is a correlation between the high homocysteine and one of these two vitamins. What is the step?

MR. BEATON: The step is establishing the mutual relationship, and that is done in the patent by the presentation of evidence of the relationship between elevated homocysteine and the vitamin deficiencies.

* * * *

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLORADO

Civil Action No. 99-Z-870

METABOLITE LABORATORIES, INC.
a Colorado corporation,
and COMPETITIVE TECHNOLOGIES, INC.,
a Delaware corporation,

Plaintiffs,

vs.

LABORATORY CORPORATION OF
AMERICA HOLDINGS
d/b/a LABCORP, a Delaware corporation,

Defendant.

LABORATORY CORPORATION OF AMERICA HOLDINGS' ANSWER AND COUNTERCLAIMS TO FOURTH AMENDED COMPLAINT

Filed October 2, 2001

Defendant Laboratory Corporation of America Holdings ("LabCorp") responds to the allegations contained in plaintiffs' Fourth Amended Complaint and Jury Demand as follows:

* * * *

16. LabCorp admits that the '658 patent includes at least one claim which states: "A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of: assaying a body fluid for an elevated level of total homocysteine and correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate." LabCorp further admits that the '658 patent includes independent claims 13 and 18 and that plaintiffs

have asserted these claims against LabCorp, and that the Court has held on summary judgment that claim 13 does not directly cover LabCorp's performance of the single homocysteine test (706994). Except as expressly admitted, the allegations of paragraph 16 are denied.

17. LabCorp admits that test 706960 is performed by LabCorp and the test results of homocysteine, methylmalonic acid, 2-methylcitric acid, and cystathianine are communicated to the physician along with information from which these results may be correlated with the presence or absence of deficiencies of cobalamin or folate. Except as expressly admitted, allegations of paragraph 17 are denied.

* * * *

FIRST AFFIRMATIVE DEFENSE

224. LabCorp has not infringed, induced, or contributed to the infringement of U.S. Patent No. 4,940,658 ("the '658 patent") because Plaintiff Metabolite has licensed LabCorp under the '658 patent, which license has not been terminated.

SECOND AFFIRMATIVE DEFENSE

225. In view of the history of the prosecution of the application resulting in the '658 patent, and the cancellation of claims and amendments made during prosecution of said application, the '658 patent as finally allowed may not be properly interpreted to read upon or include any assays for homocysteine used, offered for sale, or sold by LabCorp on which LabCorp has not paid royalties. Furthermore, plaintiffs are estopped by virtue of the doctrine of prosecution history estoppel (including but not limited to amendments and representations made to the United States Patent and Trademark Office specifically in order to distinguish the prior art and to obtain the patents) to rely on the doctrine of equivalents in order to obtain the scope for the patent as broader than the language of the claims.

THIRD AFFIRMATIVE DEFENSE

226. The '658 patent is invalid, unenforceable, and/or void for failure to comply with 35 U.S.C. §§ 102, 103, and 112. Claim 1 and dependent claims, claim 13 and dependent claims and claim 18 and dependent claims of the '658 patent are invalid under 35 U.S.C. § 103 in view of, but not limited to, material prior art and other information which indicates that the alleged invention that is the subject of the '658 patent would have been at least obvious to a person of ordinary skill in the art at the time the alleged invention was made. Claims 13 and 18 and their dependent claims are invalid under 35 U.S.C. § 112 ¶¶ 1&2 for insufficient written description and nonenablement. Claims 13 and 33 are invalid under 35 U.S.C. § 102(b) because the alleged invention claimed therein was disclosed in Refsum et al. (1985).

FOURTH AFFIRMATIVE DEFENSE

227. LabCorp has not contributorily infringed the '658 patent. The assays for homocysteine performed by LabCorp, on which royalties have not and are not being paid, are a staple article or a commodity of commerce suitable for substantial non-infringing use. LabCorp does not know that assays for homocysteine are especially made or especially adapted for use in an infringement of the '658 patent.

FIFTH AFFIRMATIVE DEFENSE

228. The plaintiffs have misused the '658 patent by over-broadly and impermissibly construing its claims to cover assays for homocysteine not falling within any claim of the '658 patent and asserting the '658 patent against those who perform assays for homocysteine that do not fall within any claim of the '658 patent so as to cause anticompetitive effect. Plaintiffs know that LabCorp and others perform homocysteine assays using a competitive enzyme immunoassay that is not covered by any claim of the '658 patent. Plaintiffs know that it is not good medical practice to use a single assay of homocysteine to determine deficiencies in cobalamin or folate. Plaintiffs know that LabCorp and others do not

correlate assays for homocysteine with deficiencies of cobalamin or folate. Yet, plaintiffs continue to assert the '658 patent against LabCorp and others who use the competitive enzyme immunoassay. Furthermore, Plaintiffs have knowingly and intentionally used the '658 patent to obtain royalties on assays that are not covered by the '658 patent. The '658 patent is unenforceable as a result of plaintiffs' misuse of the patent.

SIXTH AFFIRMATIVE DEFENSE

229. The '658 patent is invalid in view of the inequitable conduct committed during the prosecution of the application that led to the issuance of the '658 patent. Applicants filed the application leading to the issuance of the '658 patent without disclosing and providing to the Patent Examiner information of which they were aware that was material to the patentability of the inventions claimed in the application, including but not limited to Kang (1979), Wilcken (1981), Rosenberg (1983), and Brattstrom (1984). Additionally, applicants did not file an information disclosure statement and provide copies of prior art until almost two and one half years after filing the application and after the Patent Examiner had issued the first Office Action, and after the applicants had filed their first amendment arguing that: (1) "it was not previously known that elevated levels of homocysteine correlate with cobalamin and folate deficiency, nor was it suggested to use assays of total homocysteine and methylmalonic acid to diagnose and distinguish between these deficiencies," and (2) Mudd (1969) did not support the Patent Examiner's obviousness argument because the infant who had elevated levels of homocysteine had normal B12 levels and was therefore not suffering from a B12 deficiency. At the time applicants made those statements to the Patent Examiner, applicants had not provided the Examiner with copies of the material prior art. Applicants later provided the Patent Examiner with some prior art, but withheld articles by Wilcken, Rosenberg, Brattstrom, and others and buried a two-page Hoey article in over 500 pages of publications, a

significant number which were not prior art nor were particularly material to patentability. The prior art articles that applicants withheld were material to the patentability of plaintiffs alleged invention. Applicants did not point out the prior art that contradicted their earlier statements to the Patent Examiner so that the Patent Examiner would allow the '658 patent to issue. Also, in response to the Patent Examiner's rejection of claims 1-12 under 35 U.S.C. § 103 for obviousness, applicants made arguments that were contrary to what the prior art taught and did not provide the Examiner with the material prior art of which they were aware, including Kang (1979). Kang taught the step of claim 1 of adding a reducing agent such as 2-mercaptoethanol to a sample to be measured for total homocysteine. Applicants were aware of Wilcken, Rosenberg, Brattstrom (1984) and Kang (1979) because Allen and Stabler had cited these articles in their publications prior to the issuance of the '658 patent. Applicants withheld this material information with the intent to deceive the Patent Examiner in allowing the claims of the '658 patent to issue.

SEVENTH AFFIRMATIVE DEFENSE

230. Plaintiffs' claims for breach of contract and fraud which arose prior to the applicable statute of limitations period or which plaintiffs knew of or reasonably should have known of prior to the applicable statute of limitations period are barred by the statute of limitations.

EIGHTH AFFIRMATIVE DEFENSE

231. Plaintiffs' claims for breach of contract are barred by laches, waiver or estoppel. With respect to LabCorp's alleged breach for failing to certify royalty reports, plaintiffs have accepted LabCorp's royalty reports and payments for more than eight years without complaint and knew or should have known that the reports were not certified by an officer of LabCorp. LabCorp has relied on plaintiffs' acceptance of these reports and requiring certification of prior reports would be an undue burden. Plaintiffs claims for any unpaid

royalties going back more than two years from the date of this Fourth Amended Complaint are also barred by waiver, laches or estoppel in view of Article 3.03 of the Agreement which only requires LabCorp to maintain records pertaining to each royalty period for only two years in sufficient detail to permit the determination of royalties payable under the Agreement. Plaintiffs have unduly delayed in asserting claims for alleged past unpaid royalties.

NINTH AFFIRMATIVE DEFENSE

232. Metabolite's claims for copyright infringement are barred by the statute of limitations, 17 U.S.C. § 507.

TENTH AFFIRMATIVE DEFENSE

233. Metabolite impliedly, if not expressly, licensed LabCorp to use Metabolite's alleged copyrighted works.

ELEVENTH AFFIRMATIVE DEFENSE

234. Any use by LabCorp of Metabolite's alleged copyrighted works was and is a fair use.

TWELFTH AFFIRMATIVE DEFENSE

235. Metabolite has breached its duty of good faith and fair dealing under the Agreement and, therefore has materially breached the Agreement, by filing and maintaining this action against LabCorp, including Metabolite's assertion claims of breach of contract, patent infringement, copyright infringement, and fraud against LabCorp.

THIRTEENTH AFFIRMATIVE DEFENSE

236. Factual statements in Plaintiff Metabolite's patient report are not copyrightable subject matter.

FOURTEENTH AFFIRMATIVE DEFENSE

237. Plaintiffs' claims for breach of contract relating to any untimely payments for Licensed Assays for the NHL laboratories of LabCorp or for untimely payments for test no. 706994 prior to 1998 are barred by accord and satisfaction, or alternatively compromise and settlement, because Lab-

Corp has paid and Plaintiffs have accepted payment for those Licensed Assays.

FIRST COUNTERCLAIM
(DECLARATORY JUDGMENT OF NONINFRINGEMENT)

238. Upon information and belief, plaintiff Metabolite Laboratories, Inc. ("Metabolite") is a Colorado corporation having a place of business in Denver, Colorado.

239. Upon information and belief, plaintiff Competitive Technologies, Inc. ("CTI") is a Delaware corporation having a place of business in Fairfield, CT and owns or has owned U.S. Patent No. 4,940,658.

240. This claim is pursuant to the Federal Declaratory Judgment Act, 28 U.S.C. § 1331 for a declaratory judgment that LabCorp has not infringed and does not infringe any valid claim of the '658 patent, that the '658 patent is invalid and/or unenforceable and that LabCorp has not breached the Agreement with Metabolite.

241. This Court has jurisdiction over the parties to this counterclaim, all of who are presently parties to this litigation, pursuant to 28 U.S.C. §§ 1131 and 1338. The amount in controversy exceeds the sum of $75,000.00, exclusive of the interests and costs. Venue is appropriate in this forum.

242. There is an actual and justiciable controversy between the parties concerning the infringement, validity and/or enforceability of the '658 patent arising under the Patent Act, 35 U.S.C. §1 et. seq.

243. Prior to November 20, 1985, Clinical Chemistry published an article by H. Refsum et al which taught one of ordinary skill in the art a suitable method for use in determining levels of the total amount of homocysteine present in both free and complex forms in urine or blood of humans.

244. In 1969, Dr. McCully proposed that some form of homocysteine was involved in the pathogenesis of vascular disease, including coronary heart disease.

245. In 1969, The Lancet published a letter by J.G. Hollowell et al. which correlated a deficiency of cobalamin in a patient with elevated levels of homocysteine and cysteine-homocysteine mixed disulfide in the patient's urine. Hollowell et al also suggested in the letter that above normal levels of homocystine may be due to vitamin B_{12} deficiency.

246. In 1977, The American Journal of the Medical Sciences published an article by A.J. Greico which recommended routine screening of urine for homocystine as an important step in the prevention of accelerated atherosclerosis and occlusive vascular disease.

247. In 1982, the Journal of the Royal Society of Medicine published an article by Hoey et al. which taught that deficiencies of cobalamin result in abnormally raised levels of homocystine and the homocysteine-cysteine mixed disulphide.

248. In 1982, the Journal of the Royal Society of Medicine published an article by Hoey et al. which taught that assays of methylmalonic acid and assays of components of total homocysteine ("total homocysteine" as defined by the '658 patent), homocystine and the cysteine-homocysteine mixed disulphide, are useful in detecting deficiencies of cobalamin result in abnormally raised levels of homocystine and the homocysteine-cysteine mixed disulphide.

249. In 1984, Stroke published an article by Brattstrom et al. which showed that folic acid lowers plasma homocysteine in humans.

250. Prior to November 20, 1985, Metabolism published an article by Brattstrom et al. which suggests homocysteine or its derivatives might be worth considering as a risk factor for vascular disease and that folic acid therapy might be an effective prophylactic.

251. Prior to November 20, 1985, physicians had prescribed folic acid as a treatment for their patients who were diagnosed with diseases or inherited defects based on results of assays that determined the level of homocysteine in the patients' blood.

252. Prior to November 20, 1985, a person of ordinary skill in the art would have known and understood that assays for total homocysteine described in the 1985 Refsum et al. article published in Clinical Chemistry assist in determining deficiencies in cobalamin or folate.

253. Prior to November 20, 1985, physicians prescribed folic acid as a treatment for their patients who were diagnosed with deficiencies of folate based on results of assays that determined the level of homocystine and/or cysteine-homocysteine mixed disulfide in the patients' blood or urine.

254. Prior to November 20, 1985, physicians prescribed cobalamin as a treatment for their patients who were diagnosed with deficiencies of cobalamin based on results of assays that determined the level of homocystine and/or cysteine-homocysteine mixed disulfide in the patients' blood or urine.

255. As originally filed, the application, which issued as the '658 patent, contained claim 13 which did not include a step of "correlating an elevated level of total homocysteine in a body fluid of warm-blooded animals with a deficiency of cobalamin or folate."

256. In response to a rejection from the patent examiner of unpatentability over prior art, the named inventors of the '658 patent amended originally filed claim 13 to add the step of "correlating an elevated level of total homocysteine in a body fluid of warm-blooded animals with a deficiency of cobalamin or folate."

257. The only assays performed by LabCorp which plaintiffs accuse of infringing the '658 patent are the assays performed as test nos. 706994, 374983, and 716290.

258. The assays for total homocysteine performed by LabCorp as test no. 706994 using Abbott's immunoassay method, which plaintiffs accuse of infringing the '658 patent, do not include the step of combining a sample containing homocysteine with an internal reference standard comprising a known amount of homocysteine, labeled with a suitable marker.

259. The assays for total homocysteine performed by LabCorp as test no. 706994 using Abbott's immunoassay method, which plaintiffs accuse of infringing the '658 patent, do not include the step of adding sufficient reducing agent to insure randomization of the labeled and unlabelled homocysteine present in the sample.

260. The assays for total homocysteine performed by LabCorp as test no. 706994 using Abbott's immunoassay method, which plaintiffs accuse of infringing the '658 patent, do not include the step of measuring the relative amounts of labeled and unlabelled homocysteine with a mass spectrometer.

261. The assays for total homocysteine performed by LabCorp as test no. 706994 using Abbott's immunoassay method, which plaintiffs accuse of infringing the '658 patent, do not include the step of calculating the ratio of labeled to unlabeled homocysteine present in the sample.

262. The assays for total homocysteine performed by LabCorp as test no. 706994 using Abbott's immunoassay method, which plaintiffs accuse of infringing the '658 patent, do not include the step of deriving the amount of unlabeled homocysteine present in the sample.

263. The assays for total homocysteine performed by LabCorp as test no. 706994 using Abbott's immunoassay method, which the plaintiffs accuse of infringing the '658 patent, do not include any step that is equivalent to the step of combining a sample containing homocysteine with an internal reference standard comprising a known amount of homocysteine, labeled with a suitable marker.

264. The assays for total homocysteine performed by LabCorp as test no. 706994 using Abbott's immunoassay method, which the plaintiffs accuse of infringing the '658 patent, do not include any step that is equivalent to the step of adding sufficient reducing agent to insure randomization of the labeled and unlabeled homocysteine present in the sample.

265. The assays for total homocysteine performed by LabCorp as test no. 706994 using Abbott's immunoassay method, which the plaintiffs accuse of infringing the '658 patent, do not include any step that is equivalent to the step of measuring the relative amounts of labeled and unlabeled homocysteine with a mass spectrometer.

266. The assays for total homocysteine performed by LabCorp as test no. 706994 using Abbott's immunoassay method, which the plaintiffs accuse of infringing the '658 patent, do not include any step that is equivalent to the step of calculating the ratio of labeled to unlabelled homocysteine present in the sample.

267. The assays for total homocysteine performed by LabCorp as test no. 706994 using Abbott's immunoassay method, which the plaintiffs accuse of infringing the '658 patent, do not include any step that is equivalent to the step of deriving the amount of unlabelled homocysteine present in the sample.

268. The assays for total homocysteine performed by LabCorp as test no. 706994 using Abbott's immunoassay method, which the plaintiffs accuse of infringing the '658 patent, do not include any step of correlating an elevated level of total homocysteine in a body fluid with a deficiency of cobalamin or folate.

269. The assays for total homocysteine performed by LabCorp as test no. 706994 using Abbott's immunoassay method, which the plaintiffs accuse of infringing the '658 patent, do not include any step that is equivalent to the step

of correlating an elevated level of total homocysteine in a body fluid with a deficiency of cobalamin or folate.

270. LabCorp does not encourage others to use the assays for total homocysteine performed by LabCorp as test no. 706994 using Abbott's immunoassay method, which plaintiffs accuse of infringing the '658 patent, to correlate an elevated level of total homocysteine determined by the assay with a deficiency of cobalamin or folate.

271. The assays for total homocysteine performed by LabCorp as test no. 706994 using Abbott's immunoassay method on which royalties have not and are not being paid do not infringe any valid claim of the '658 patent and are not covered by any valid claim of the '658 patent.

272. As a direct and proximate result of plaintiffs' assertion of the '658 patent against LabCorp, LabCorp has suffered irreparable damages, including but not limited to injury to its reputation and good will in an amount that cannot be ascertained and which cannot be adequately compensated by monetary relief alone.

273. The damage or injury to LabCorp is continuing and will continue until enjoined by this Court.

274. Upon information and belief, plaintiffs' actions in wrongfully asserting the infringement claim have been and are knowing and willful.

SECOND COUNTERCLAIM
(DECLARATORY JUDGMENT OF INVALIDITY)

275. Paragraphs 238-254, above, are incorporated herein by reference.

276. The claims of the '658 patent are invalid for failure to comply with the following requirements of the Patent Act, 35 U.S.C. § 1 et seq., 35 U.S.C. §§ 102(b), 103(a) and 112 ¶¶ 1&2.

277. Claims 1 and dependent claims are invalid under 35 U.S.C. § 103 for being obvious in view of Marcela et al.,

Anal. Biochem. (1985) 150:58-66 and Kang et al., Pediatric Research, Vol. 13, pp. 1141-43 (1979) or Saetre/Rabenstein (1978). Marcell teaches the method of claim 1 without the step of adding the reducing agent and Kang et al teaches the specific reducing step of claim 1. Dependent claims 2-12 are also obvious because they recite insubstantial elements that are also obvious to one of ordinary skill in view of Marcell, Saetre/Rabenstein, and Kang et al.

278. Claims 13 and 33 of the '658 patent are invalid under 35 U.S.C. § 102(b) based on Refsum et al., Clin. Chem. Vol. 31, No.4 (1985) because Refsum et al teach a method for assaying for total homocysteine and suggest using such method to determine diseases in humans relating to homocysteine metabolism. A person of ordinary skill in the art would have known before November 20, 1985 that such diseases included cobalamin or folate deficiency.

279. Claims 13 and dependent claims of the '658 patent are invalid under 35 U.S.C. § 103 as being obvious over the prior art including anyone of the following publications (Trugman et al. (1985) or Greico et al. (1977) or Higginbottom et al. (1978) or Hoey et al. (1982) or Hollowell et al. (1969) or Mudd (1969), or Bevan (1982) or Freeman et al (1975) or Trugman et al. (1985) in view of Saetre/Rabenstein (1978) or Refsum et al. (1985).

280. Claims 13 and dependent claims are also invalid under 35 U.S.C. § 112 ¶ 1 because the specification does not contain a sufficient written description or enable one of ordinary skill in the art to practice the claimed invention, which requires the steps of assaying for an elevated level of total homocysteine and correlating the elevated level of total homocysteine with a deficiency of cobalamin or folate. Total homocysteine can be elevated for a number of reasons, including renal diseases, B_6 deficiency, inherited disorders of metabolism, thyroid hormone deficiency, and the effects of certain common drugs, including cancer drugs.

281. Claims 13 and dependent claims are also invalid under 35 U.S.C. § 112 ¶ 2 because the claims do not particularly point out and distinctly claim the subject matter which Allen et al. regard as their invention. Because homocysteine can be elevated for a number of reasons other than a deficiency of cobalamin or folate and because a person may be deficient in cobalamin or folate and not have an elevated level of total homocysteine, one of ordinary skill cannot simply assay for an elevated level of total homocysteine and then correlate with a deficiency of cobalamin or folate.

282. Claims 18 and dependent claims are invalid under 35 U.S.C. § 103 as being obvious over the prior art including Hollowell et al. (1969), Hoey et al. (1982) or Higginbottom et al. (1978) or Trugman et al (1985) in view of Refsum et al. (1985). Hollowell, Hoey and Higginbottom teach the use of assays for homocysteine and methylmalonic acid together to determine deficiencies in cobalamin or folate. Refsum et al teaches a method for assay total homocysteine and teaches its use for determining diseases involving homocysteine metabolism, which include cobalamin and folate deficiencies. Norman (1982) teaches use of assays of methylmalonic acid to determining deficiencies in cobalamin.

283. Claims 18 and dependent claims are also invalid under 35 U.S.C. § 112 ¶ 1 and 2 because assays for homocysteine and methylmalonic acid cannot distinguish between deficiencies of cobalamin or folate because if both homocysteine and methylmalonic acid are elevated, then a deficiency of cobalamin or cobalamin and folate may exist. Also, homocysteine can be elevated for reasons other than deficiencies of cobalamin or folate and methylmalonic acid may be elevated for reasons other than cobalamin deficiency so that assays of total homocysteine and methylmalonic acid cannot be used to detect and distinguish between deficiencies of cobalamin or folate or both.

284. As a direct and proximate result of plaintiffs' assertion of the '658 patent against LabCorp, LabCorp has suffered irreparable damages, including but not limited to injury

to its reputation and good will in an amount that cannot be ascertained and which cannot be adequately compensated by monetary relief alone.

285. The damage or injury to LabCorp is continuing and will continue until enjoined by this Court.

286. Upon information and belief, plaintiffs' actions in wrongfully asserting this lawsuit have been and are knowing and willful.

THIRD COUNTERCLAIM
(DECLARATORY JUDGMENT OF PATENT MISUSE)

287. Paragraphs 238-286 above, are incorporated herein by reference.

288. The plaintiffs have misused the '658 patent by over-broadly and impermissibly construing its claims to cover assays for homocysteine not falling within any claim of the '658 patent and asserting the '658 patent against LabCorp and others who perform assays for total homocysteine that do not fall within any claim of the '658 patent so as to cause anticompetitive effect. Plaintiffs have used the '658 patent to require LabCorp and others to pay royalties on assays that are not covered by the '658 patent.

289. Upon information and belief, before asserting the '658 patent against LabCorp and others, plaintiffs knew that, prior to November 20, 1985, doctors used the results of assays of total homocysteine, including elevated levels of total homocysteine, to diagnose or treat certain diseases or inherited defects in their patients.

290. Upon information and belief, before asserting the '658 patent against LabCorp and others, plaintiffs knew that, prior to the alleged invention by the named inventors of the methods claimed in the '658 patent, doctors used the results of assays of total homocysteine, including elevated levels of total homocysteine, to diagnose or treat certain diseases or inherited defects in their patients.

291. Upon information and belief, before asserting the '658 patent against LabCorp and others, plaintiffs knew that, prior to November 20, 1985, doctors had prescribed folic acid as a treatment for their patients who were diagnosed with diseases or inherited defects based on results of assays that determined the level of homocysteine, including elevated levels of homocysteine, in the patients' blood.

292. Upon information and belief, before asserting the '658 patent against LabCorp and others, plaintiffs knew that, prior to the alleged invention by the named inventors of the methods claimed in the '658 patent, doctors had prescribed folic acid as a treatment for their patients who were diagnosed with diseases or inherited defects based on results of assays that determined the level of homocysteine, including elevated levels of homocysteine, in the patients' blood.

293. Upon information and belief, before asserting the '658 patent against LabCorp and others, plaintiffs knew that, prior to November 20, 1985, doctors had prescribed cobalamin (vitamin B12) as a treatment for their patients who were diagnosed with diseases or inherited defects based on results of assays that determined the level of homocysteine, including elevated levels of homocysteine, in the patients' blood.

294. Upon information and belief, before asserting the '658 patent against LabCorp and others, plaintiffs knew that, prior to the alleged invention by the named inventors of the methods claimed in the '658 patent, doctors had prescribed cobalamin (vitamin B12) as a treatment for their patients who were diagnosed with diseases or inherited defects based on the results of assays of homocysteine that determined the level of homocysteine, including elevated levels of homocysteine, in the patients' blood.

295. Plaintiffs know that LabCorp and others perform assays for total homocysteine using a competitive enzyme immunoassay that is not covered by any claim of the '658 patent.

296. Plaintiffs know that it is not good medical practice to use a single assay of homocysteine to determine deficiencies of cobalamin or folate.

297. Plaintiffs know that the results of more than 50 percent of the assays of total homocysteine do not yield an elevated level of total homocysteine.

298. Plaintiffs know that LabCorp and other laboratories do not correlate assays for total homocysteine with deficiencies of cobalamin or folate. Yet, plaintiffs continue to assert the '658 patent against LabCorp who uses the competitive enzyme immunoassay to assay levels of total homocysteine.

299. Plaintiff CTI has demand and received royalties from laboratories who perform single homocysteine assays not using a gas chromatography/mass spectrometry method and which do not correlate an elevated level of total homocysteine with a deficiency of cobalamin or folate.

300. Plaintiff CTI has demanded and received from at least one clinical laboratory royalties on single homocysteine assays which are not performed using gas chromatography and mass spectrometry and which do not yield an elevated level of total homocysteine.

301. Plaintiffs demand that LabCorp pay plaintiffs royalties on each single homocysteine test (706994) performed using Abbott's immunoassay method.

302. The '658 patent is unenforceable as a result of plaintiffs' misuse of the patent.

303. As a direct and proximate result of plaintiffs' assertion of the '658 patent against LabCorp, LabCorp has suffered irreparable damages, including but not limited to injury to its reputation and good will in an amount that cannot be ascertained and which cannot be adequately compensated by monetary relief alone.

304. The damage or injury to LabCorp is continuing and will continue until enjoined by this Court.

305. Upon information and belief, plaintiffs' actions in bringing this lawsuit to recovery royalties to which they are not entitled have been and are knowing and willful.

PRAYER FOR RELIEF

WHEREFORE, LabCorp prays the Court grant it the following relief, including:

A. Judgment dismissing, with prejudice, plaintiffs' Complaint;

B. A declaration that LabCorp has not infringed or contributed to infringement of any valid claim of the '658 patent, that the patent is invalid and/or unenforceable and that the Agreement is void and unenforceable;

C. A declaration that plaintiffs have misused the '658 patent and that the '658 patent is unenforceable.

D. An injunction enjoining plaintiffs and any parties in active concert therewith from asserting the patent or instituting or prosecuting any lawsuit or other legal proceeding seeking in any way to enforce or maintain the '658 patent against LabCorp or its customers;

E. That this case be declared exceptional within the meaning of the Patent Act, 35 U.S.C. § 285, and that LabCorp be awarded its costs and reasonable attorneys' fees incurred in connection with the matter;

F. An award of attorneys' fees and costs under 17 U.S.C. § 505.

G. That all issues of fact be tried by a jury; and

H. Such other and further relief as the Court may deem just and proper.

Respectfully submitted this 1st day of October, 2001.

/s/ John P. Higgins

John P. Higgins
(N.C. State Bar #17442)
Alston & Bird, LLP
Bank of America Plaza
101 South Tryon Street
Suite 4000
Charlotte, NC 28280
Telephone: 704/444-1000

and

James A. Jablonski, Esq.
DC Box-004
Gorsuch Kirgis LLP
1515 Arapahoe St.
Tower I, Suite 1000
Denver, CO 80202
Telephone: 303/376-5000

Dow N. Kirkpatrick, II
(Ga. State Bar #423900)
Alston & Bird LLP
One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3424
Telephone: 404/881-7000

Attorneys for Defendant Laboratory Corporation of America Holdings, Inc.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLORADO

Civil Action No. 99-z-870

METABOLITE LABORATORIES, INC., et al.,

Plaintiffs,

vs.

LABORATORY CORPORATION
OF AMERICA HOLDINGS,

Defendant.

REPORTER'S [TRIAL] TRANSCRIPT

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Voir Dire Examination of Prospective Jurors

[Page 75, lines 3-7]

MR. JABLONSKI [Counsel for LabCorp]: * * * And this is a very impressive jury, very well-educated.

THE COURT: Tremendously. * * *

* * * *

Dr. Sally Stabler—Direct

[Page 180, line 3 to Page 182, line 5]

BY MR. WHITEHAIR:

Q. Have you had occasion to make a list of the traits that you desire when you're investigating a potential diagnostic test?

A. I did.

Q. Did you prepare a list?

A. I did.

Q. Let me have you turn to the small notebook, the very first document, Exhibit Demo 1.

MR. WHITEHAIR: And this, for the record, is a demonstrative. And I believe your Honor has already explained that these won't go back to the jury room.

THE COURT: All right.

BY MR. WHITEHAIR:

Q. We have it open in front of us. Are you going to be—

A. Unfortunately, Dr. Stabler doesn't.

All right.

Q. Before we look at it, what generally were you trying to capture in putting together a list of traits?

A. These are all the things that go in your mind when you actually think about a test that could be a good test diagnostically. If you were to write a manuscript about what you did, these are the kind of points that the referees would expect you to sort of address; that yeah, this would be a good thing, this would work.

Q. All right. Let's just start through. And you directed all the contents of this document. Right. This is your work?

A. Yeah.

Q. No. 1, readily found.

A. Well, it has to be easy to measure, and it needs to be in something you can get easily. And that would be blood and urine.

Q. What are some other options that are hard—

A. Well, you know, for hepatitis, they do liver biopsies often. And they stick a needle in your liver. And it just doesn't work out for routine testing to do that kind of thing.

Q. What does it mean to have it reliable?

A. Reliable is if you do it on this blood sample and that number you get, you believe that number, it always comes out to be that number. If you do it again, you're going to get the same sort of number.

Q. And that probably leads us to No. 3, stable.

A. Yeah. This is really crucial, because there is a lot of changes in blood once you take it out of somebody's body. And if the thing you want to measure disappears in the next minute or so, you know, tough luck; you're not going to—that's not going to be a test. So you want it to last definitely for minutes but best is if it will last for hours.

Q. There is a reference here to constant while healthy.

A. Again, you want—if I measure this thing in a person today, I want to get almost the same number that I got yesterday, if the person is still in the same state of health. And next week, I should get the same number. It should be a very small range of the values that I'm going to get.

* * * *

[Pages 202, line 22 through Page 203, line 14]

THE COURT: Be seated, please.

Members of the jury, I read to you yesterday what an expert or opinion witness is. It's a person who has specialized knowledge by scientific, technical, specialized training that will assist the trier of fact, the jury, to understand the evidence. And that type of witness, an expert or opinion witness may testify in the form of an opinion.

The Court will accept Dr. Stabler has an expert or opinion witness in the areas of hematology, oncology, internal medicine, metabolic medicine as to B12 and folate,

and the area of the state of prior art at the relevant time of this patent. Those areas of expertise.

Is there anything else you want to—

MR. WHITEHAIR: I think we were also talking about what treating physicians do with the tests in her area of expertise.

THE COURT: Well, she may testify to that as long as it falls within one of the fields of expertise.

* * * *

[Page 204, line 1 to Page 209, line 3]

Q. We left off with your testimony late yesterday in the middle of an exhibit. Why don't we return to that exhibit and ask to you turn to the first small book with the white cover, first exhibit. We call it Demo 1 but it has a tab 1. Do you have that in front of you, "desirable traits of a useful diagnostic test"?

A. I do.

Q. We've gone over the first three, and I think we were in the—finishing up with 4 before we jumped on. Why don't we just go back. Talking about "constant while healthy." What do you mean by constant—or relatively constant, I think is the word you use in the exhibit?

A. What I mean is that if you measure something with this test while the patient was healthy, there would be a really tight range of values that you would get. The value from yesterday would be very similar to what you got today or what you get next week.

Q. Well, isn't—I'm sorry if I interrupted. Isn't that a problem with something like a glucose test? Doesn't that vary all day?

A. Well, it can, which is why they usually use fasting glucose, because that's much—you get much tighter numbers if you do it at the same time of the day.

Q. What do you mean by fasting level?

A. Before you eat anything in the morning.

Q. Let's talk about "correlates," the next one. Now, this appears to be a little more formal definition than the other ones you described. Is that because I asked to you use the judge's clarification or interpretation of the patent word "correlates"?

A. Correct.

Q. Let's translate that into the way in which you use these terms and phrases in your search for a desirable or a useful diagnostic test. What do you mean by "correlates"?

MR. HIGGINS: Objection, your Honor. He said that it related to your interpretation of correlate, but I don't believe it has the complete definition of "correlation" as your Honor expressed in the Court's order.

THE COURT: We'll go into that later. The objection is overruled. She may answer.

BY MR. WHITEHAIR:

Q. Let's just talk about how it works for you in your day-to-day work.

A. Well, what I say there is the marker correlates mutual or reciprocal relationship with the disease state compared with the healthy state. And to use an example, like we were using the diabetes example, there, a mutual relationship would be that the elevated blood sugar or blood glucose correlates there with the diagnosis of diabetes. You if you have diabetes. The reciprocal would be if the blood sugar is actually normal, then you don't have diabetes.

Q. How—how does a doctor decide if something is elevated, when you talk about this term "elevated"?

A. Well, that's addressed somewhat in No. 6.

Q. Okay.

A. Because—for each person, see, has their own value, which—while they're healthy. So that they would stay, like I

said, in the tight values. They would stay at that same number. It wouldn't vary very much. But when they get the disease state, it will be elevated for them.

A lot of times you don't have the luxury of having previous tests, and then you're stuck with comparing the person against some kind of a reference range. There is lots of names for those, and that's determined by looking at the numbers that you get from a big group of people who you think are all normal; and, you know, we call that reference range, normal range, population range. There is just a whole bunch of terms.

Q. Let's turn to this measurable difference from healthy. What are you capturing here?

A. Well, this is the ideal test, is that you have all of the normal values for a person. Like I said, if you kept doing maybe yearly a test, like they do for glucose for people that it's staying at a certain nice, low level; but if the person then develops diabetes, there is now such a big jump in the number that there is no question that there is a difference between the normal state and the disease state. And it's great when you have individual persons.

But what we do when you don't have serial levels like that is that again we have to study a disease population, so you would study a group of people who all have diabetes, like for the glucose, and compare the numbers you get there, that range, against the numbers you got in a group of people who were normal. And what you are really hoping when you design these tests is that this is a really big difference, there is no overlaps, and that it will be easy to see whether the value is in the diseased vs. in the normal.

Q. What do you mean by "treatment available"?

A. That's medical bias here, is that, you know, we're doctors and we want to be able to fix things, so is it good to know something bad, like a high blood sugar? If there is no treatment, most patients don't really want to know bad news that doesn't have a treatment. And most doctors don't want

to know that, and it's actually hard to get tests paid for that don't—that don't lead to you doing something, some constructive action.

Q. "Predicts outcome."

A. That's the same sort of medical bias, where the answer really has to mean something. It says—it directs you that—to say that, Oh, I know, I found this high level, like if, say, the child is so bad with diabetes that they're in a coma, you find this really high glucose level. Say a high level, a really high level, would be 800. You find that and you say, Oh, boy, as soon as I give insulin, this patient will wake up. And you know that that high level predicts what will happen. And so those are the kinds of tests that you want.

Q. "Early warning system"?

A. And again, that's a big medical bias—is that if you're already so ill, so impaired by the time the test is positive, then people aren't that enthusiastic about being tested for it. The best tests show you early on in the course of a disease in preclinical states like we talked about yesterday that something is going wrong. And then if it's a good test that has treatment available, then you're going to do something about it before it's too late.

Q. I take it a diagnostic test is useless, then, if it comes back normal or unelevated.

A. No. No. That's what we do. We do tests in order to figure out which of the things that we suspect are true. When a patient comes to see a doctor, they don't say, Give me this test, usually. They say, I have these symptoms. And while you're talking to them, examining them, you get the differential diagnosis. That's the term of you think what's the most likely cause, No. 1, No. 2, No. 3. And then all our tests are directed to saying, Well, how I will exclude each of these, so that if the test comes back negative, you just cross it off. Okay. And then you start dealing with the other things that are still on the list. And that's how we arrive at a final diagnosis. That's how we do it.

* * * *

[Page 226, lines 21-23]

MR. WHITEHAIR: Pardon me, your Honor. I believe—It's in our laps. Let's look at it here, specifically Demo Exhibit 2 in the small book.

* * * *

[Page 228, line 3 to Page 230, line 6]

THE WITNESS: So I want you to focus here on this line, because this is the central part of the whole pathway. And homocysteine is—these are all amino acids, which is the name of the kind of little compound they are. And homocysteine can get converted to methionine by that enzyme. And this is where you need the folate and the vitamin B12. When that happens, you use methionine for itself. You need it. But also, it gets activated. This is another enzyme. Once it's activated, it participates in hundreds of reactions. It's very crucial that you have that. After it does those reactions, it's converted to something else, something else, and converted down to homocysteine again. So now we have a circle. We've actually recycled that homocysteine. But homocysteine is at a branch point, so it could go one way, or it could go this way. When it goes this way, it goes through a couple reactions. It turns into cysteine, which is another one of the amino acids that you need, and that can be broken down. And you just—what you don't need just comes out in your urine. This is really sort of one way, that way; and this is a circle.

BY MR. WHITEHAIR:

Q. Thank you. Did you also prepare an illustration that helps us understand the different states of the body that might be processing this pathway?

A. That's correct, because people have been studying which way it's going to go—it's called the regulation—for decades.

Q. Let me have you then take up Exhibit 3A, and in the jury books it's Exhibit 3. They don't have the A on any of the original demonstrative exhibits. That's just for the blowups. Go ahead and tell us what you're trying to show here, Doctor.

A. Now, you also need methionine. You eat methionine. It's in your food. But what about when you're not eating, overnight, or fasting? You still have to have this crucial activated methionine. So when this has been studied, it turns out that the methionine—I've abbreviated it "meth," and the homocysteine—this is a standard abbreviation, H-C-Y-S—just circles around a number of times before it goes down the branch point. That's how you conserve your methionine. Now, say you eat methionine. And there is a lot of methionine in high protein foods, so I'm using as an example steak dinner, where you will get a whole lot of methionine. So here you'll activate it, you'll run the reactions you need until you're down to homocysteine again; but at this point, see, the body is really in balance. It's regulated and something tells it I've got plenty of methionine, let's get rid of it. And it will go through all these reactions to cysteine, and all the extra goes out in your urine. And this is happening all the time, every day, back and forth to keep it all in balance.

* * * *

[Page 232, line 17 to Page 233, line 9]

Q. Let's turn on Exhibit 4 and ask you if that's the chart that you prepared.

A. I did.

Q. That shows at least of these three topics; that there is checkmarks in the methionine list; right?

A. Correct.

Q. And one is cysteine?

A. Correct.

Q. And this indicates that lack of a known role of homocysteine?

A. That's right.

Q. Given all this, was your lab looking for a diagnostic marker to determine vitamin deficiency?

A. To just use as a test, no. But yes, like I said, we want to understand the pathways. You know, it's more global than just have a test. We want to know what's going on when you perturb these pathways.

* * * *

[Page 234, line 21 to Page 235, line 6]

Q. What was your working theory on what would be subnormal or what would be happening in your measurement tests on this pathway?

A. Well, we had to go with what people had been speculating, which would be that methionine would be low because that's what the prevailing theories were; that that was very important.

Q. Was there actually a study out that you were relying on for that?

A. Yeah. We did read a study from a Dr. Parry which—

Q. P-A-R-R-Y?

A. Right.

* * * *

[Page 235, line 19 to Page 236, line 7]

Q. Just take a quick look at that, just to confirm that this is the study you relied upon.

A. So No. 35, the title of it is "Serum Valine in Methionine Levels in Pernicious Anemia under Treatment," by T.E. Parry. I can read the first part of a paper—like this has a summary, usually, or an abstract. So if you read in that first part a sentence sort of near the bottom says, "The serum

methionine level is subnormal in pernicious anemia in relapse." Relapse means not being treated. "It rises to normal in 48 hours after treatment," so it's low; and then it went to normal after they got their treatment.

Q. All right. Now, then they reference that methionine levels actually correct with B12 and folate?

A. That was the gist of this paper.

* * * *

[Page 236, line 13 to Page 239, line 19]

Q. * * * Did you put together a list of the possible metabolic changes that you and the lab were considering when you undertook your experiment?

A. I did.

Q. And let's just look at the first of a series in Exhibit 5. And these are just for your lap. We'll call these laptop exhibits. Exhibit No. 5. Why don't you walk us through. It looks like there is two different statements on there. Why don't you just tell us what this is about.

A. At the top, I've written, "Possible Metabolic Changes." And No. 1 is just to remind you what this pathway is; that the homocysteine in purple there. By action of this enzyme in the circle, you see it shows that it needs B12 and folate, is changed to methionine, and that if everything is just right, there would be just a normal level of the amount of methionine, homocysteine, and cysteine that would be present. It would just be what—a baseline level.

Q. What are you showing in No. 2 below?

A. Well, No. 2—now, the red in that block is supposed to say, now, if you're B12 or folate deficient, then that enzyme will be blocked, see. It doesn't have the partners. It's not going to work as well. So the two things there that we're showing that might result is that methionine would be down because you're not making it and the homocysteine would be high because you've blocked changing it from

homocysteine to homocysteine to methionine. But cysteine would be just the way it is, normal.

Q. Did you try to consider any other possible changes?

A. We did.

Q. Let's turn to the next exhibit and explain the number 3 that you added.

A. I've repeated No. 1 and 2 here on the page so you can look at it simultaneously. But No. 3, you have this block, so the homocysteine is not going to be—to the methionine. But what if that branch point gets more active? The enzymes that carry homocysteine away by changing it to cysteine, they could get a lot more active. They could pick up the slack, in which case methionine would still be low but now cysteine would be high because you're making more cysteine. And then—but the homocysteine is now going to be normal because the—those other processes that make cysteine have taken it away.

Q. Okay. So is that pretty much all the options that you have in this kind of a pathway?

A. No.

Q. Go on. Let's—we're going to go to No. 4—No. 7, but we have this in blowup so you can perhaps make some more illustrative comments, so we don't we have us take a month to reset our thing. This is Demo Exhibit 7A for the record. And Dr. Stabler, if you'd just confirm for us that this is simply a blowup of what you were just looking at as Exhibit 7.

A. Correct.

Q. Why don't you go ahead and tell us. You've picked us another path.

A. These are the ones that we've already talked about, the possibilities; but I over simplified. It turns out there is another enzyme that can do this reaction, homocysteine to methionine. And this enzyme doesn't need B12 or folate. It

uses this stuff called betaine instead to do it. So people had speculated—and it's totally possible—that this enzyme, which would just kick in when this was blocked, the B12 and folate dependent one—when that was blocked, instead this enzyme would pick up the slack. If that happened, you wouldn't expect any changes. Homocysteine, methionine, homocysteine, cysteine, they're all just going to be the same.

Q. Recapping your exhibit, what tends to be the most likely outcome if you look at these choices? What was your working hypothetical?

A. Sorry.

Q. What was your working hypothesis going in?

A. I bet that methionine would be low. I mean I had to believe what other people were saying and had been writing about it for years, so I thought methionine would be low. Of course, we hoped there would be other changes. We wanted as many as possible. We hoped that homocysteine would be high.

Q. How about cysteine?

A. Same thing. There really wasn't that much known about cysteine changes, so that I reserved judgment. Didn't know.

* * * *

[Page 247, line 14 to Page 248, line 1]

Q. Think back to your Exhibit 7, which showed all the possible metabolic changes you recall with the black circles and the three red circles. The bottom one had the betaine pathway. You were basically balancing out which of these things was the most likely of those four pathways, the stable state, the second third and fourth. Which one did you find now with this lab discovery?

A. We didn't find any of them, because the only abnormality we found was that total homocysteine was elevated. And we didn't find that methionine was changed.

Q. Was this a bad result for you?

A. No. It posed problems in having to try to explain to other scientists why methionine was not low. * * *

* * * *

[Page 248, line 4 to Page 252, line 18]

Q. You made some comment about this earlier. Was homocysteine going to be an easy marker to try to track and manage in this process?

A. No. Because of its chemical structure, it means that it's actually hard to handle in the lab.

Q. Let's set this down, have you go back in. And we're going to turn to a couple of charts about these sulfur bonds just so we understand why it's complex. We don't need—I think this section is not designed to teach everybody all about biochemistry but just to understand this complication. Let me have you turn to Exhibit 33 in the big book. And we're going to use 34 in a minute. And really, all I want you to do is just look at these red Ss. The rest of the chart, we could come back to some other day. But right now, I just want to know if these red Ss are going to help you explain why the total homocysteine test was a challenging test to undertake and to use.

A. That's right. If you look on this chart, you see that we've listed the—under the word compound, we list homocysteine and cysteine and albumin. And each one has an S there. That's a sulfur. When you combine it with an H like that, it's a sulfhydril. And the problem with these sulfhydrils is they don't like to be by themselves. They're always wanting to combine with another sulfhydril or something else.

Q. Albumin: What is that?

A. Albumin is a protein that thickens your blood. The reason plasma is thick is because it has a lot of this albumin dissolved in it.

Q. And it's got a bunch of sulfur on it?

A. And it has all these sulfhydril groups, these SHs.

Q. And what's Exhibit 34 designed to illustrate?

A. It's to show you the way homocysteine is actually traveling in blood, because it's not staying by itself. There is incredibly small quantities of just the homocysteine with that SH group that you saw on the previous page. Instead, what you have is listed here on this left side is a compound. The top one is two homocysteines find each other, and their sulfhydrils bind together. Now you see that they make this sulfhydril link or bridge, SS. See the red? And that's two of them together. And that's what we call homocystine. It's a disulfide, two sulfide, disulfides, of homocysteine. Then you have two of them. And there is hardly any of that. Look over to where we say the percent of total—and by total there, I mean total homocysteine.

Q. Not total of everything in the serum?

A. No. Total of how much homocysteine that there would be, all the kinds; and it's really low. It's under 1 percent, and then you can get an actual concentration. See, we use this slide for when we give the talks to the doctors. That's why I put the concentrations there. Okay. Then under it is one that shows that the homocysteine often makes a disulfide with cysteine. That was the other thing we measured. That's called homocysteine cysteine disulfide, and you could see the two Ss there.

Q. Can we just call that MDS from now on?

A. You could.

Q. Okay.

A. And there is more of that. There is about 30 percent. Here we got 28.4 percent. So there is more of that than homocystine. Then the rest appears mainly to be bound to those groups on albumin onto that protein because it has these sulfhydrils sticking out and it sort of just sops up

homocysteine. Am that's actually the bulk of it. And here I have it as 71 percent. Now, these things aren't static. They appear to be changing. They're changing partners in your blood while you're living, and then they also change once you take the blood out of somebody.

Q. Why don't you measure one of these three? Do you need to measure them all? What's the story there?

A. Well, what had been determined was that their changes are so marked after you take the blood out of somebody that things disappear. It looks like the things that are the homocystine or the mixed disulfide sort of disappear in time from that blood sample, especially if you start freezing and thawing it, and it all ends up on the protein. And that's what caused all these problems in saying what is a normal concentration of homocystine, plus look how little there is of homocystine.

Q. So when you try to measure it, then, in your labs, were you trying to catch every single one of these?

A. That's the whole concept of a total homocysteine, is that you can sort of standardize the situation by releasing it from protein, releasing it from those bonds, and let's get it all. And then it won't matter if—how long we leave that blood sitting on the bench, how many times it was frozen. All these little things that could have a huge impact on it don't matter if you decide I'm going to measure it all.

Q. Is that why the patented discussion typically talks about total homocysteine?

A. What we did was total homocysteine. That's right. That's what we do.

Q. Let's put some chemistry behind us for a while. You talked about these scattergrams. You found this homocysteine jumping out several stories high. Was this just corroborating or showing what had already been done in the literature before?

A. Nobody had measured total homocysteine in a patient with B12 or folate deficiency.

Q. So did you go ahead and publish this information?

A. That's right. We again submitted an abstract to the same meeting. But now it was 1985, and I presented it in December in '85. It was published in the abstract book.

Q. And let's just turn, just to hold our spot—Exhibit 40 is the abstract of the '85 conference you attended?

A. Yes.

Q. How did this presentation go this year?

A. Oh, maybe there was a little bit more interest but not much. Again, you see the doctors who were doing vitamin B12 research and then the general doctors who attend this meeting also just to learn and keep up—they really were satisfied with vitamin B12 levels and with folate levels as, you know, the diagnostic be-all. That's what it was. And so again: All right, but why do you want a new test?

* * * *

[Page 252, line 25 to Page 253, line 17]

Q. And just for the record, you published this in the Journal of Clinical Investigation, Exhibit 41?

A. That's correct.

Q. All right. So I take it that since there was really no response to you, the logical next step was to give up on this direction. This test wasn't going anywhere. What did you do next?

A. That wasn't quite how we thought. We thought that the test was so good in Dr. Lindenbaum's gold standard patients and was even—you saw that those infrequently treated patients were often abnormal before they had any other symptoms, so we thought now we have tools to tell whether the patients who have much less classic abnormalities due to B12 deficiency or folate deficiency, or their

vitamin levels are only a little bit low or actually normal, below normal, or there were just a host of questions that could then be answered by using these tests, total homocysteine, methylmalonic acid, to show a deficient state.

* * * *

[Page 255, lines 6-20]

Q. What did you think you had that deserved a patent?

A. The first time that anyone showed that the total homocysteine correlated with B12 or folate deficiency, and that the study, like the study—Dr. Lindenbaum's neurologic—that was in the New England Journal of Medicine. That's the best medical journal—showed that it was useful in patients who had atypical problems and that would be missed by your standard diagnostic methods that were in use then.

Q. Was there also a specific proposed method for measuring total homocysteine in serum?

A. And that's right. We also—our method was different than the couple of other methods that had been described. And ours was very good because of using an internal standard so that we could take care of those problems of all those sulfhydrils getting together while you were preparing the blood.

* * * *

[Page 280, line 5 to Page 281, line 9]

Q. All right. So our elevated numbers comes back. And what does—let's just take in the total homocysteine case. You've ordered the single total homocysteine test, it comes back elevated. We'll just pick a high number so that it's not a big fight here. What does the doctor then do next?

A. The doctor will prescribe vitamin therapy.

Q. And what therapy will the doctor describe—prescribe?

A. Completely depends on that patient's story, their history, what vitamins were they already taking. Very common that someone comes in who is already taking a multivitamin. If they have a high total homocysteine, you're going to give them vitamin B12. You know they're already getting folate, so the doctor is going to individualize.

Q. What it—what if the patient has no history of taking any supplementation?

A. I think now that most doctors are giving both, both folic acid and vitamin B12, because there is so much in the medical literature in the last couple years about the benefits. Even though they haven't yet been ironclad proven, there is so much out there saying that people will benefit if they have their total homocysteines lowered. And the best way to do it is to give them both folic acid and vitamin B12.

Q. Are you talking about giving these people shots for the rest of their lives?

A. Well, I think the reason it's been popularized is because we have figured out that you can use high-dose pills of vitamin B12.

Q. Actually you can take it in your mouth?

A. You can take it—even the worst-case patients of pernicious anemia can be treated with vitamin B12 pills.

* * * *

[Page 303, line 3 to Page 305, line 18]

MR. WHITEHAIR: Would you mind, Mr. Zuckerman, so I make sure it's accurate, because it's a little bit different than the notes that I wrote.

THE REPORTER: "Let's switch gears a little. The defendant in this case, LabCorp, has suggested that the total homocysteine only test is widely used for a broad array of things other than to determine a patient's vitamin deficiency levels. What's your reaction to that?"

THE WITNESS: I don't agree with it. I think that there are many CONDITIONs that are associated both with having the B12 or folate deficiency and an elevated total homocysteine.

BY MR. WHITEHAIR:

Q. Well, I understand there is a number of conditions that appear to be associated with elevated total homocysteine. What do you say to that?

A. I SAY that the underlying thread, the thing that links them, is that they're associated with either B12 or with folate deficiency.

Q. Did you take some time to put together a chart based on your own assessment of the different mechanisms that lead back to this vitamin connection?

A. I did.

Q. The jury doesn't have it, and I want you to describe it. Under our rules, it needs to be discussed before it can be put in front of them, or it may not be able to put in front of them; so if you would just work with me through what we call a foundation of an exhibit. You have a copy of what's been marked for identification as Exhibit 8 in front of you.

A. Yes.

Q. Tell me what—what were you trying to accomplish in this exhibit?

A. I was trying to explain the cause for having a vitamin deficiency. THERE S really three mechanisms where you get to have a vitamin deficiency and how that related to each of the conditions that has been seen in—with elevated total homocysteine, also.

Q. Let's talk about the mechanisms, and then we'll talk about the conditions. What are the mechanisms that you see in this vitamin deficiency scenario?

A. Having a poor diet is the most common cause probably of folate deficiency, because it's found mostly in fruits and vegetables or organ meats, and a lot of people don't eat

those, so that diet has always been incredibly important as a cause.

Q. What else?

A. Then you—you can have problems absorbing vitamins. There is known abnormalities of the stomach and the intestines which cause you not to take in the vitamin, even though you're eating plenty of it in your food.

Q. Are there any other mechanisms?

A. And then there are substances that you it can ingest or conditions you can have where the vitamin does not work optimally, and we call it sort of a vitamin defect, in that the enzyme is inhibited or the vitamin is in the wrong form, or a lot of different problems like that.

Q. Now, for each—were there any other substantial mechanisms you could think of?

A. Those are the main—I would say those are the main ones.

Q. Now, you laid those against each of the conditions that have been suggested as associated with elevated total homocysteines. Is that right?

A. Uh-huh.

Q. And you laid them out here and checked off the condition and each of the mechanisms that was implicated?

A. Correct.

* * * *

[Page 309, line 23 to Page 312, line 21]

Q. I want you to take a moment, Doctor. I want you to look at all seven of these. And I want you to tell me whether in your opinion these are conditions that are diagnosed by a total homocysteine test.

A. No.

Q. The doctor doesn't take the test to see how old their patient is?

A. No.

Q. What sex they are?

A. No.

Q. Whether they've been smoking?

A. No.

Q. Whether they've been drinking?

A. No.

Q. Does the doctor know what the medications are?

A. That's parts of the history—

Q. Will the doctor—

A. —to know, yes.

Q. What about this kidney disease?

A. Well, there are special tests for kidney disease.

Q. This is not a test—

A. Creatinine, BUN, yeah. You don't get this test.

Q. Is it among the tests you might use?

A. No.

Q. How about for thyroid disease?

A. No, not at all.

Q. Let me ask you to turn to the next chart. Did you compare—did you put together a list of what was—when the total homocysteine test was useful?

A. Yes.

Q. And let's turn to Exhibit 9. And going down each of these, I think you're just reiterating what you said. 1 through 7 are all nos, and then you've got two—we were sly. They're green. Tell me what 8 and 9 mean.

A. You use the total homocysteine to detect B12 deficiency and folate deficiency and/or both.

Q. All right. Now, did you also compile a list of the select manifestations, the various things that are caused by B12 and/or folate deficiency?

A. I did.

Q. And where will we find that?

A. That is the No. 10 demonstration.

Q. Well, not to belabor it, but I—you've been talking for most of the day about a variety of conditions that get called out in anemia. You talked about some tingling hands. Is this an attempt to try to capture most of those?

A. These would be the manifestations that a person could have if they were B12 or folate deficient.

Q. And that's what's under the—

A. That's on all — all of these different things is what is seen in various patients who have the deficiency.

Q. And then the recommended treatment?

A. You treat the deficiency.

Q. You've listed neural tube defects near the bottom. What are those again?

A. Those commonly called spina bifida. People may have heard that word, and it's problems that happen in the spinal cord in the nervous system really early in pregnancy. And it's clearly related to whether the mother has enough folate in her body and is getting enough daily, very early in her pregnancy, when she gets pregnant.

Q. You listed heart attacks here.

A. Well, that's what all this vascular disease association shows. If you can actually measure serum folate in a group of people like they did for the nurses health study and those—well, there they looked at the intake. But in a Cana-

dian study, they actually measured the serum folate. And the people of the low serum folate or the people who don't eat the folate, they have higher risk of having heart attacks. That's why everyone is so excited, because there is something we can do about it.

Q. And the same issue for strokes?

A. And the same thing is true in strokes. They show that in the NHANES study.

* * * *

[Page 322, line 19 to Page 323, line 14]

Q. Let me ask you this question: What if a company in the business of selling assays for total homocysteine made the following statement to the doctors ordering the tests: This test is intended to be used as an independent risk factor for vascular disease and is not intended for the diagnosis of folate or vitamin B12 deficiency. Do you consider that good medical practice?

A. I do not.

Q. What's wrong?

A. Well, if I ordered that test on a specific patient, the test comes back, it's high, what do I do then? I say, oh, this test—this total homocysteine doesn't show that you're vitamin deficient because it's the way this test is used. So I don't offer therapy? I just let it be? I let it be high, instead of treating with the combination, or one or the other, depending on everything else I know about the patient, and say I'm sorry, bad news, you have a risk factor?

Q. What's your medical opinion about a doctor who would fail to treat in response to that high homocysteine level?

A. I think right now people would think, and I would agree, that that's actually malpractice.

* * * *

[Page 324, lines 13-25]

Q. Let's turn to Exhibit 66 in the big book. And tell us what this article is from and what it tries to teach.

A. This is from the JAMA, Journal of the American Medical Association, that comes out weekly. It's very widely read. And it's August of this year, 2001. See that there at the bottom? And it was written—you could see there is a big list of authors, and it includes people from University of Colorado—excuse me—University of California and then people from the big nutrition center in Tufts that's very highly regarded, as well as people from the Harvard School of Public Health and an international expert even from the Netherlands, plus other authors; so it's a big, collaborative effort of a lot of different authors.

* * * *

[Page 327, line 13 to Page 328, line 19]

Q. Just the conclusion. Those four lines.

A. "In the meantime, since combined therapy with folic acid and cyano-cobalamin is well-tolerated, it is reasonable to consider routine therapy in men older than 45 years and women older than 55 years."

Q. And on the front page—were you reading from the back?

A. Yes.

Q. I'm sorry. If you would read the conclusion section on the front page, starting, "Folic acid," and then when you go through it tell us what CHD means.

A. Okay. This is in the abstract in the front page.

"Conclusions: Folic acid and cyanocobalamin supplementation may be cost-effective among many population subgroups and could have a major epidemiologic benefit for primary and secondary prevention of CHD," coronary heart disease, "if ongoing clinical trials confirm that homocysteine lowering therapy decreases CHD event rates."

Q. Thank you for that. And what are these homocysteine lowering therapies?

A. They are combinations of vitamin B12 and folic acid. That's what they refer to in this study, but it could also be vitamin therapy, one or the other.

Q. What's your opinion of the relationship between total homocysteine and vitamin B12 and folate status in a human being?

A. I think they're intimately linked.

Q. You're crossing your fingers?

A. Yeah. They go together like this.

Q. Other than to determine vitamin deficiency, is there any other substantial use you know of for ordering a total homocysteine test?

A. No.

* * * *

Dr. Sally Stabler—Cross

[Page 458, line 24 to Page 459, line 3]

Q. But that's not something you or Dr. Allen discovered, is it?

A. Renal disease? No, we discovered that vitamin B12 and folate deficiency correlates with an elevated total homocysteine.

* * * *

[Page 492, line 5 to Page 494, line 4]

BY MR. HIGGINS:

Q. Dr. Stabler, I'll read from the order here on the word "correlating" of Claim 13. It says that correlating—"The term 'correlating' in Claim 13 is a verb that is construed to mean 'to establish a mutual or reciprocal relationship between.' Okay. Do you understand that?

A. Okay. Uh-huh.

Q. And it says—it further says, "that describes a discrete step in a sequential process." So my question is once a body fluid is assayed for total homocysteine and the result is elevated, what step is performed that falls within the definition of "correlating" as I've just read it to you?

A. Losing me again here. The mutual relationship is that you see that if the level of total homocysteine is elevated that there is a deficiency of cobalamin or folate.

Q. Well, the definition says to establish a mutual or reciprocal relation, and that describes a discrete step in a sequential process. So what step takes place to establish that an elevated level is—has a mutual or reciprocal relationship with a deficiency of cobalamin or folate?

A. Well, if you had already done the total homocysteine on someone and later you did it again and it was higher, then you would know that the step would be that you would compare the first one to the second one and say it's now higher, so this person now has a deficiency of cobalamin or folate.

Q. So in order to establish this relationship, it requires that a patient's homocysteine be measured twice?

A. That—that would be one use that you did it. That's how you would know for one particular person it might be elevated. But you might not have done it twice. That's one example of how you would do it. Other ways, you would compare it against what you know in the literature to be considered elevated.

Q. So it's your testimony that by obtaining an elevated—an elevated level of total homocysteine that you can look at the literature and determine that that elevated level for a particular patient is the—has a mutual or reciprocal relationship with a deficiency of cobalamin or folate?

A. That's in general how you would do it.

Q. And so does that take place in the mind of the physician?

A. Well, yeah. The physician will be—is the person who is going to be looking at the number, yes.

Q. And so you're saying that it's sufficient to establish a mutual or reciprocal relationship between an elevated level of total homocysteine and a deficiency of cobalamin or folate by looking at medical literature?

A. Wait. Start over with that one again.

Q. I'm just asking –

A. No, I mean "establishing a relationship"? The literature tells us that elevated total homocysteine is a—seen in cobalamin or folate deficiency. I mean there is reams of that.

* * * *

[Page 506, line 18 to Page 507, line 16]

Q. Well, let me ask you this: What is the minimum that is required to establish an elevated level of total homocysteine with a deficiency of cobalamin or folate?

A. The minimum? The minimum what?

Q. What is the minimum act or step that a physician can take to establish that an elevated level of total homocysteine has a mutual or reciprocal relationship with a deficiency of cobalamin or folate?

A. They have to see the level, and then they have to make the correlation that if they—they have to decide against whatever standard it is they're going to be using whether they think it's elevated or whether they think it's normal for this patient. And then if they think it's elevated, they say this shows that there is a deficiency of either one of these. If they say that I've decided that this is normal, then they say I don't see a deficiency of either vitamin B12 or folate.

Q. And is that all that done in the physician's mind?

A. Everything is done in the physician's mind.

Q. So in other words, to fall within the second step of Claim 13, all—all that is required is a mental step?

A. It's—there is no surgery involved or no—I can't—how can I answer that? Everything you do, you read something, it's a mental step. You—I don't know—I don't know what that means.

* * * *

Dr. Sally Stabler—Redirect

[Page 519, line 20 to Page 520, line 3]

Q. To your knowledge—oh, I see. To your knowledge, Dr. Stabler, based on all the things you've discussed since you started here—to your knowledge, did anyone ever suggest measuring total homocysteine in those circumstances?

A. No.

Q. In fact, before the prior art dated November, 1985, had anyone ever correlated an elevated total homocysteine level with a deficiency of vitamin B12 or folate?

A. No.

* * * *

Frank McPike—Direct

[Page 553, lines 15-20]

Q. Was CTI at any point in that time taking the position that homocysteine was a marker for vascular disease?

A. No. It's always been a marker for vitamin deficiency. I guess the good news was that this was another—another disease indication that could utilize the services of this diagnostic text—test.

* * * *

Frank McPike—Cross

[Page 565, lines 17 to 21]

Q. And as a matter of fact, CTI claims that LabCorp performs, when it performs the single homocysteine only test, even utilizing the Abbott method—CTI claims that that activity is covered by claim 13; correct?

A. That's correct. That's correct.

* * * *

[Page 572, lines 20 to 24]

Q. Now – and the statement as contained in this press release dated January 5, 1999, is consistent with your position, which is that every single homocysteine test done in the United States, CTI is entitled to a royalty on?

A. Yes.

* * * *

Frank Ryan—Direct

[Page 610, line 6 to Page 611, line 10]

BY MR. WHITEHAIR:

Q. Do you use the term "diagnose"? Do you know—do you have a view of what that word means?

A. I've—I know what the word means, I think.

Q. Do you know what the word—do you consider that be synonymous with the word "correlate"?

A. No.

Q. How would you distinguish those, Doctor?

A. Well, diagnose. If somebody has prostate cancer and you go and take out the prostate and you identify that they have cancerous cells in their prostate, you've made a diagno-

sis that there is prostate cancer. If a person like the—C-reactive protein is a test that cames out in the last couple years that looks like one of the better monitors for heart disease. And there is a correlation between the level of C-reactive protein and the chance that you'll have a heart attack in five years, I think is what it says. So there is a correlation. There is no diagnosis there. We haven't made a diagnosis. We're just correlating the chance that somebody will have heart disease, so it's not a diagnosis.

Q. Do you know if there is any therapy available in response to C-reactive protein?

A. C-reactive protein, I would say that things that reduce inflammation in your body would lower your C-reactive protein. I think that like aspirin would probably be good for that.

Q. Do you see the word "correlation" meaning something more to do with probabilities and the word diagnosis more to do with facts of finding a disease?

A. Yes. Correlation is much more like probability.

* * * *

Frank Ryan—Redirect

[Page 620, line 14 to Page 621, line 4]

Q. Now, back in '96, when you were doing these tests—this test, you didn't test for folic acid then, did you?

A. No.

Q. Instead, you just ordered the single homocysteine only; right?

A. Yes.

Q. And you found your level was right in the middle of the reference range?

A. Well, pretty close.

Q. So you took folate; right?

A. Yes.

Q. And the homocysteine level came down?

A. Yes.

MR. WHITEHAIR: That's all I have.

* * * *

Robert Allen—Direct

[Page 646, lines 14-25]

THE COURT: I have explained to the jury what an expert or opinion witness is. And at this time, the Court will accept Dr. Allen as an expert witness in the areas of internal medicine, hematology, and the science and medicine of B12, folate, and homocysteine. And I think these broad areas will cover. And then if you have specific questions and there is an issue of whether it falls within the area of his expertise, I'm going to ask the attorneys to come up to the bench again. I'm not—I don't think it's necessary to qualify him in the area of state of the art. If he is knowledgeable in the main areas and is able to testify about the state of the art, he may do so. And if there is a question, the attorneys can come up to the bench.

* * * *

[Page 684, line 23 to Page 685,line 9]

BY MR. WHITEHAIR:

Q. Do you know what was written at the time about assays of this—in this area, in, say, 1985 time frame?

A. I'm familiar with what textbooks taught about the diagnosis of B12 and folate deficiency, the use of various tests that were in existence and what practicing physicians knew about and what tests they utilized to diagnose B12 and folate deficiency.

Q. Have you compiled that information in the slide materials that you said preceded this lawsuit?

A. I have a series of slides that I've prepared long before this lawsuit started that I've used for many years in giving talks about this particular topic.

* * * *

[Page 687, line 7 to Page 695, line 13]

Q. I interrupted the order of your presentation. Would you go back to Exhibit 87 now.

A. I have that one.

Q. Where are these quotes or—I guess they're all quotes. Where are they from?

A. Well, they're from the chapter on megaloblastic anemia, from Harrison's Principles of Internal Medicine. And the next exhibit, Exhibit 88, has the Tenth Edition and the Eleventh Edition of those chapters. On the slide, the quotes are from 87, but the exact identical quotes occur in the '83 edition.

Q. Why don't you go back, then, to 87—pardon me—and go through this for us.

A. It starts by saying they're teaching that the finding of significant macrocytes—this is big red cells. Remember the normal population range is 80 to 100, and they're saying if it's above that, this suggests the presence of megaloblastic anemia—that can be B12 or folate deficiency. If the macrocytosis is marked, the MCV is greater than 110, the patient is much more likely to have a megaloblastic anemia. The second statement: It should be emphasized that occasionally, not very often, but occasionally neurologic disease may occur with a patient with a normal hematocrit. Hematocrit is also a measure of the number of red cells. So it's saying occasionally you can have problems in a patient that is not anemic. In the last statement, it says, "The normal range of vitamin B12 in serum is 200 to 900. Values less than a hundred indicate clinically significant deficiency." In other words, the B12 test is so good that if you're deficient in your

body, your B12 level won't be just below 200 but it's going to be below 100 if this is of any significance.

Q. What's the next step?

A. I think we've already talked about the two chapters. If we go to exhibit there—Exhibit 88. If we go to 89, we see now a leading textbook for the practice of family medicine. This was published in 1984. And the next exhibit, which is Exhibit 90, has that chapter from which these quotes are taken.

Q. How do you pronounce his name?

A. I would pronounce it Rakel.

Q. R-A-K-E-L?

A. That's correct. I might mention that the authors of this chapter are two professors from the University of Utah. The preceding exhibit was written by two authors, a professor from Harvard and a professor from Tufts Medical School in Boston. So here the textbook is teaching that "the diagnosis of pernicious anemia should be suspected in the elderly individual who develops macrocytic—" that's big red cells "—megaloblastic anemia while consuming a normal diet. Oval macrocytes—" I showed you examples of those on the blood smear "—are the characteristic abnormality in the blood, and their presence results in a greatly increased value for the MCV," not just over a hundred but much above that. "The anemia varies in degree, but the blood hemoglobin level is less than 7 or 8." Normal is about 12 to 16 in symptomatic patients. "Finally, in vitamin B12 deficiency, serum vitamin B12 is greatly reduced, less than a hundred, whereas the serum folate is normal."

Q. What's your next exhibit?

A. Well, after we get past the Rakel chapter, we now have quotes from a textbook of hematology in 1987. This is by Dr. Jandl.

Q. That's J-A-N-D-L?

A. That's correct.

Q. And our exhibit number is?

A. Well, for the quotes is 91 and for the textbook chapter from which the quotes are taken, it's 92. Dr. Jandl is also a professor at Harvard Medical School. He starts out: "The MCV is usually over 115 but commonly 130 to 150. The white count—" these are the white cells that fight infection "—ordinarily is between 3,000 and 4,000 cells per microliter." Normal is in the range of 5- to 10,000. "Platelet counts are subnormal in nearly all patients." These are the little cells that help our blood clot. LDH stands for lactic dehydrogenase. That's an enzyme that's present within red blood cells in the bone marrow. In either B12 or folate deficiency, it's released in the blood. So he's teaching that LDH levels average about 15 times normal in megaloblastic anemia. And then, finally, "Concentrations of serum B12 below a hundred indicate vitamin B12 deficiency sufficient to cause megaloblastic anemia." Now, in this chapter, which I didn't put on the slide back in the 80's, there are two other important statements. First deals with the serum folate level. And it states that the serum folate level, the normal range is 6 to 20. Patients with folate deficiency have values below 3. A similar statement is made in Harrison. 6 to 20 is normal. Below [4] in folate deficiency. Dr. Jandl also explains in great detail about methylmalonic acid, how it's a very sensitive indicator of B12 deficiency, known since the 50's, and goes on to say that this test is, quote, "seldom necessary," end quote.

We go past 92, which is the Jandl chapter. We come to the last quotes from a textbook. This is from Cecil, Textbook of Medicine, 1985, by professor Beck, another Harvard professor.

Q. And what's the exhibit number?

A. For the quotes, it is 93; and Dr. Beck's chapter in Cecil is Exhibit 94. "Neurologic symptoms occur later in some but not all patients. Curiously, they can occur in the

absence of megaloblastic anemia." "A decreased serum vitamin B12 level is decisive diagnostic evidence. Clinical signs generally appear when the serum level is below 80 to 100 picograms per milliliter." "Methylmalonic aciduria—" that's increased methylmalonic acid in urine "—is also a sensitive index of vitamin B12 deficiency." "In practice, assay of urinary methylmalonate is rarely necessary." So that the common theme of the textbooks in the mid 80's is that you suspect B12 or folate deficiency when you have just not big red cells but really big red cells. You have a very significant anemia. You will have a low white blood cell count. You'll have a low platelet count. And the critical test, the gold standard, is either the serum B12 or the serum folate. And in patients with clinically significant disease, the values for these tests are not just below the population normal range, they are way below the population normal range.

Q. What's the use of the MMA test?

A. Well, it existed. It had been known since about 1955. It was known to be a sensitive indicator. But as both Dr. Jandl and Dr. Beck said, it was either seldom necessary, rarely used; and I never used the test, and I don't know of anyone at Washington University or at the University of Colorado that used urinary methylmalonic acid to diagnose even a single patient.

Q. Did you have any personal experience with the way in which these standards might have been used?

A. Well, I have no doubt that informed physicians not only read these teachings but they followed them. And I have three personal examples. The first is one of our CU medical students who did a medical rotation at one of the private hospitals in Denver—I think it was Saint Joseph's—who then took a medicine rotation at University Hospital. The question came up whether a patient might be B12-deficient. And he said, Oh, he had learned that when you think about B12 deficiency, you look for the LDH level. This is a test that's—not only is it made in red cells but it's—can be elevated in heart disease and liver disease. Very

common a patient in the hospital will have had the LDH measured regardless of the disease. And he said he had learned that you don't even think about B12 deficiency unless the LDH is at least three or four or five times normal. The second example: One of the general internists at University Hospital considered by many to be the finest general internist. Most of the faculty went to see him. In the mid 80's, I discussed with him—he realized how important B12 deficiency was. He looked for it. And when he found a patient that he suspected of being deficient and the B12 level came back, let's say 150, clearly below 200 but not below 100 where clinically significant disease occurs, he wouldn't treat the patient. He would follow, get a B12 every six months; and when the B12 level, if it got below 100, then he would institute treatment. Third example is a hematologist at the VA hospital, who at morning rounds one time when the question of B12 deficiency came up, he stated that he never suspected or worked up a patient for B12 deficiency unless the MCV was over 110. When I challenged him on that, he went into the textbooks. And so those are three personal examples of real physicians following the teachings of the text books at the time.

Q. What was the folate teaching at the time?

A. Well, as I said, the folate teaching was again that the hematologic presentation was the same as B12 deficiency: You look for big red cells, they had to be really big, you needed anemia, and the test that told you whether the patient was deficient or not, the perfect test was the serum folate level, not just low but very low.

Q. In 1985, did your research team have an opinion about these teachings?

A. Well, I would say we were—usually don't read chapters in textbooks about your own specialty. I mean if you're an expert in B12 or folate deficiency, you don't—You spend your time looking up chapters on diseases you're not an expert in. We were certainly, however, suspicious that some of these concepts, at least, were inaccurate; and if you

look back through the textbooks, you won't find any documentation for any of these statements. Hematology textbooks in particular, Dr. Jandl's chapter, will have 3- or 400 references. And if you look for these statements, you either won't see a reference after it; or if you do see a reference and you read it, it doesn't really say. And I think what these doctors were doing is they were—they were expressing their beliefs based on their personal experience. And we were suspicious, particularly Dr. Lindenbaum, who had been collecting cases, as Dr. Stabler said, for 20 years. He was sure that every patient didn't have a B12 below 100. And he pointed out to us that there had never been a good clinical study of B12 deficiency since the early 20's. Once the disease could be cured, no one collected large numbers of patients and described what the clinical spectrum of abnormalities was.

Q: What did your lab do next?

A. Well, we decided we would test the textbooks. And if we turn to Exhibit 95, it poses the question at the top: Are hematology and medical textbooks correct in what they teach us about the clinical spectrum of cobalamin deficiency? And there were two possible approaches: We could do the Lindenbaum approach, collect patients, study them very carefully, or we could use the new metabolic tests that we had. The most powerful way, of course, is for the three of us to get together and do both approaches at the same time. And that's what we did.

* * * *

[Page 725, line 15 to Page 726, line 11]

Q. Were the studies you've been describing in the B12 field the ones you'd just been discussing with us?

A. Yes.

Q. Is there anything similar on the folate side?

A. Yes. If we go to 126, this is a one slide summary of a study we did with Dr. Lindenbaum in patients with folate

deficiency. He had collected 100 consecutive alcoholics that were admitted to the hospital with anemia. And he then sorted out what the cause of the anemia was. Many of them were iron-deficient, but he had 37 that had anemia and had megaloblastic bone marrows. And he ruled out cobalamin deficiency. Therefore it—with other things, including response to therapy, they were clearly folate-deficient. He looked at the serum folate, the gold standard for this deficiency. In his lab, the normal was above 2.1. Only 41 percent of these clearly folate-deficient patients had low values for serum folate, whereas when we looked at the total homocysteine, back there with our very first generation assay, our cutoff was 22; and 34 of the 37 patients, or 92 percent, had elevated values of total homocysteine. So here again, the total homocysteine test was clear superior to the serum folate test.

* * * *

[Page 743, line 5 to Page 746, line 23]

Q. With regard to the second concern of the office action, what was your response back to the Patent Office?

A. Okay. The two articles cited—one was by a Dr. Mudd in 1969, concerned a patient that couldn't put a methyl group on the cobalt to make the active form of methyl B12, and so there was a problem converting homocysteine to methionine. And a form of one of these sub homocysteine—subspecies was present in either the blood or the urine. And that was combined, then, with the paper that talked about methylmalonic acid. And again, our response was here we didn't have to talk about what an imaginary person would think, because we cited, which we supplied when we filed the patent, a review article by Dr. Mudd that was cited, in which Dr. Mudd himself, in 1974, five years after his '69 article, and he knew all about all of these genetic defects. And a couple of the kids had already been described with some form of homocystine in their urine due to B12 deficiency. And he wrote and said that he didn't know if this occurrence in these real [sick] kids—whether some form of

homocystine, the two homocysteines together—whether that occurred commonly in these rare diseases, or whether it was a rare occurrence, and that he had no idea whether it ever occurred in adults with pernicious anemia.

Q. Are you describing what you provided as an attachment to the response to office action?

A. Well, I don't think we attached anything. What we did was we wrote what—why we thought the examiners were wrong. We had two of them at that point. This Mudd quote came out of a review article that we had cited in our original specification. So the examiner was already—had that and knew about that article.

Q. And you're referring now to the list of references cited in Exhibit A, on the first and second pages of that Exhibit A?

A. Yes, I am. The article in question is on the second page. And if we go down the column, we start with Malloy, and we get down to the second—second Mudd article, the one that says, "Heritable Disorders of Amino Acid Metabolism, Pattern of Clinical Expression and Genetic Variation," 1974.

Q. What was the next concern proposed by the Patent Office?

A. Well, the second office action—and it also allowed a number of the claims where we were using total homocysteine and MMA. Those were allowed. But there was still a problem—it was primarily with Claim 13 and the wording of Claim 13, whether we were trying to claim any use of total homocysteine or whether it was—it should be limited, which we thought we'd done the first time—whether it should be limited to detecting B12 and folate deficiency.

Q. Dr. Allen, would it be helpful to your testimony at this time if you could see the exhibit that had been put up by the defense that described the first form that you put in the specification and the second form in the amended claim?

A. Yes, it would.

MR. WHITEHAIR: Could I ask as a courtesy, Ms. Harris, if you could put up Exhibit MB. I believe that's the correct one.

BY MR. WHITEHAIR:

Q. You may have MB in front of you in an exhibit book, if that would be easier than seeing it.

A. I have it on my screen. I can—I can see it.

Q. All right. Okay. And what was it that the Patent Office had concern about?

A. Well, the claim as originally filed started out with a method for detecting a deficiency of cobalamin or folate in warm-blooded animals by assaying body fluids for the presence elevated levels of total homocysteine.

Now, I thought that since the first part of that claim said it was a method for detecting cobalamin or folate deficiency, we were clearly limiting our claim to just such uses.

Now, it's my understanding that sometimes when you start a claim that way, it really is a limitation. Other times—and in this case—the Patent Office said, Well, they weren't sure that was a limitation. I think they said it was an intended use. So what they said was, you know, you can only—your claim can only cover a method for detecting deficiency of cobalamin or folate. That's what we meant originally. We were never trying to claim any conceivable use of a total homocysteine assay. So the examiner helped us. The examiner said, Here is how to be absolutely certain—okay—that you—the examiner let us copy the first introduction. There is a little change. It looks like we put in the word "comprising the steps of," and then it says, "assaying a body fluid for an elevated level of total homocysteine," and then a discrete step, "correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate." And our response—I think we did—I think

it's word for word what the examiner suggested. If not, there is some little minor thing; but we agreed with the examiner, and so we amended Claim 13.

Q. And what did the United States Patent and Trademark Office do after—in response to that amendment?

A. They then allowed all the rest of the claims, including Claim 13.

* * * *

[Page 768, line 20 to Page, 769, line 8]

A. * * *. There was a rather lengthy telephone conversation, where we went through the entire what turned out to be a license agreement between Metabolite and Roche Biomedical—or actually with Hoffmann La-Roche. It covered a number of different items.

Q. Did you end up having a conversation about what you would charge if you kept doing tests in the transition period?

A. The first item—and this is a phone call that Mr. Knesel and Dr. Bookout were on the other end and I was on my end. And we sort of took things in order. The first question was if they signed a long-term agreement, would Metabolite give them a price break.

And I responded that I would be willing to lower my charge * * *.

* * * *

[Page 769, line 23 to Page, 770, line 20]

[A.] So once the agreement was signed, Metabolite would charge Roche 43 percent of whatever Roche charged their customers.

Q. Now—and that's for which kind of tests? Are they being done at Metabolite, or are they being done at Roche?

A. These are tests that would be done at Metabolite.

Q. Was there any conversation about what would happen once Roche was able to do these themselves in house?

A. Well, they were very interested in having the rights to use our automated system. And so they asked me what the charge would be by Metabolite if I turned over all of our software, all of our know-how, assisted them in setting up the assays, and also provided any kind of long-term advice or support that they needed.

And I told them that in return for that, Metabolite would like to have a second 6 percent that would go to Metabolite, would not be passed onto University Patents.

Q. And what was the response to that?

A. They thought that was just fine.

Q. Did you start working out the details?

A. Well, the last thing that came up was the issue of what if they used this robotic system for tests other than the Metabolite assays.

* * * *

[Page 771, line 15 to Page 772, line 12]

[A.] And at one point in the conversation, then, Mr. Knesel said to me—he said Dr. Allen, How much would we have to pay Metabolite when we do the metabolite tests if we can use your robotic system for any other system and we don't have to pay you a penny or even tell you about using the robotic system for any other tests?

And I said that I had never thought about it but it would certainly have to be considerably more than the 6 percent.

And Mr. Knesel then said to me, When you do the test for us, we're paying you 43 percent. How about if we do the metabolite test in house, we pay you half that, 21-and-a-half percent? And then they could use the robotic system for any other test, not pay me or not tell me anything about it.

And I thought—

Q. Let me ask: What did you do in response to that?

A. Well, I thought about it for a minute. I thought that this robotic systemic could be used for many, many different tests. I might be giving up quite a bit by agreeing to that. On the other hand, I really felt these metabolite tests were important and that their usage was going to increase markedly and I realized what a nightmare it would be to try to keep track of the others. And so I said that would be fine.

* * * *

[Page 843, line 5 to Page 849, line 21]

Q. Let me go, then, and ask you what is Exhibit 143.

A. 143 is a letter from me with certain attachments to Dr. Peter Wentz, Roche Biomedical dated June 4, 1992.

Q. And that's signed by you on the second page?

A. Yes, it is.

Q. What was—let's just refer to the first paragraph. What was—what were you trying to say there?

A. Well, just talking about our conversation and just telling him that I was glad things were running smoothly. And the second sentence is "I will always be glad to answer any technical questions that arise concerning the metabolite assays and that Dr. Stabler and myself will be glad to answer any questions that doctors might have regarding results or interpretations of the metabolite assays."

Q. Okay. Dropping down to the third paragraph, what are you describing there?

A. Oh, I'm sending him some tables and some literature reference that—I think he mentioned they were interested in coming up with a, oh—a physician education brochure. They were always from the beginning either through brochures or messages on test reports teaching patients [sic] how

to use the total homocysteine and the other metabolites to diagnose B12 and folate deficiency.

Q. With regard to the other attachments, what did you understand was the use to be made of your attachments by LabCorp—or, I'm sorry, Roche at that time?

A. They could use them or the information considered in them to prepare this physician education piece.

Q. And did that include changes on your patient report protocol?

A. There wasn't any patient protocol here, but they—as I testified earlier, they—I mean I suppose—well, they did not have permission to make any significant changes. Again, that was our report. I assume that when they started doing the tests themselves, they would have their own report.

Q. Did you write paragraph 2?

A. Yes, I did.

Q. What were you explaining to Dr. Wentz in paragraph 2?

A. Well, I could read the first couple of sentences. It says, "One aspect of the metabolite assays that I did not mention in our conversations concerns the occasional request that only one of the metabolites be performed rather than all four. I have always refused to do this because I do not believe that it is good medical practice." And then I go on to explain how I'm afraid that if at this point in time, dating back to 1988, that if you just gave many physicians just one metabolite—for example, the homocysteine—they might not understand what to do with that result. If you'll recall, in the middle and late 80's, there was really no place for a doctor to go and read about information about these tests. This didn't enter the textbooks, oh—my chapter was published sometime in late '92. The other textbooks didn't pick up on the MMA and homocysteine assays and how they should be used until the mid 90's. And as you'll also remember when Mr. Higgins was cross-examining Dr. Stabler, there was articles

published in the vascular disease literature talking about how folic acid would lower anybody's homocysteine. And I was literally terrified in these early years, not now, but in the early years, that if we just provided a total homocysteine value and the result was elevated that a doctor might just say, Oh, oh, okay. I'll just treat with folic acid. And as you heard Dr. Stabler testify, that can be incredibly dangerous if the patient is B12-deficient, because the folic acid can actually correct all of the hematologic problems, the doctor then thinks, "I made the right treatment choice," but it doesn't do anything for the neuropsychiatric problems. They can develop anew or they can progress. So I felt it was important at this point in time and earlier to make sure the doctor couldn't make a mistake. Same price, they got the total homocysteine and they got a methylmalonic acid. And so right in the interpretive report, you didn't have to suggest that he get it. It was staring the doctor in the face. And then if that MMA was elevated, the doctor would say, Oh, okay, this is B12 deficiency. Now, if it wasn't, then you could conclude that it was very likely to be folate-deficient.

Q. Did your opinion change, your medical opinion?

A. It changed, I would say—it changed gradually but certainly within a few years. I knew at this time that other—some labs were ordering single homocysteines. There wasn't anything I could do about them; but I felt for my laboratory and I hoped for Roche that they would offer at least the MMA and the homocysteine together, at least until these tests became more widely used and doctors understood how to use them.

Q. And were there any other developments that prompted a change in your medical opinion?

A. Well, again, it was primarily physician education. Another major change, though, came in the beginning in the mid 90's but really accelerated once, as Dr. Stabler testified, we showed that oral cobalamin was as or more effective than the shots. Now for the first time, a doctor could get the total homocysteine. And if the doctor wanted to, he didn't have to

order other tests or figure out which of the two vitamins was deficient; he could just prescribe a pill that had both a large amount of cobalamin and folate.

Q. Do you have any evidence to suggest that there was the confusion you've described during that time frame?

A. Yes. I think you'll see that in the next exhibit, 144.

Q. What is this exhibit, Doctor?

A. This is a fax that I sent to Dr. Wentz on August 25 of 1992, and it contains the second page is an article from the Wall Street Journal, August 19. And the Wall Street Journal article is noting an article that was published in the Journal of American Medical Association on August 19 of that year. The Journal of American Medical Association article was one that described an association between homocyst(e)ine, with the E in it. If we look at the third page of the exhibit— .

MR. WHITEHAIR: If I could, your Honor, Bates No. L00029.

THE WITNESS: I might just point out that this way of writing homocyst(e)ine was a shorthand expression for total homocysteine. You'll see that in many different articles. And it indicated that in a U.S. physician study, doctors in this country that were in the very top part of the range for homocysteine had a moderate but significant increased risk of having heart attacks. And the point of sending this to Dr. Wentz can be seen if we come back to the second page—

MR. WHITEHAIR: For the record, your Honor, L000028.

THE COURT: Why don't you just give the last 4 numbers. That's easier.

MR. WHITEHAIR: Thanks.

THE WITNESS: Okay. And if we look at the left-hand column, we'll see the article is entitled, "Certain Amino Acid Increases the Risk of Heart Attacks." And if we come down in the article to the third paragraph, it starts out, "But the risk can be offset by dietary supplements of vitamin B6 or a

related vitamin called folic acid, which help metabolize homocysteine." And it refers to Dr. Stampfer, who is a Harvard professor. And this was exactly what I was worried about in the previous letter of doing a total homocysteine. Here you have a medical article in a widely read journal talking about homocysteine and vascular disease, talking about treating with B6 and folic acid and not mentioning treatment with vitamin B12 or the dangers that could occur if you treat it, a B12 patient with folate. And if you'll recall, by this time, Dr. Stabler's elderly studies, we knew there were probably 20 million elderly people in this country that were B12-deficient.

BY MR. WHITEHAIR:

Q. Did Dr. Wentz follow-up with you?

A. Yes. The next Exhibit, 145, is a memo he sent me, again sort of responding to the article that I had sent him, suggesting that they would like to offer a—just a single homocysteine test for vascular disease; that the warning would be that if the—we're talking now about this Bates No. M1000. And if we come down and look at the—what's present in bold, the note, the second sentence, it says "If, however, the test was ordered to evaluate any unexplained hematologic abnormality, a normal or abnormal result is not conclusive. And it is recommended to order the complete megaloblastic anemia profile and then cites this article that I thought was an important article for homocysteine and vascular disease, but it was a dangerous article. And I followed up by calling Dr. Wentz and telling him that I thought this kind of note was far from sufficient; that if you wanted to offer, and they certainly could offer, a single homocysteine, but they certainly needed a much stronger warning to warn doctors that it could be extremely dangerous to treat a patient with an elevated total homocysteine with folic acid and not be aware of the important benefits from B12.

Q. What's time frame of this letter?

A. October 30, 1992.

* * * *

[Page 875, line 8 to Page 876, line 8]

THE COURT: I'm having trouble hearing you. I'm sorry. They're paying on the panel test is what he's saying.

MR. HIGGINS: We're paying on the panel test. Basically, what the plaintiffs are trying to argue is that LabCorp pays on the panel test which has a homocysteine test on it; therefore, they ought to be paying on the single test. And we went through that issue on summary judgment, and it's—it should not come out here in this trial. It's not relevant.

MR. WHITEHAIR: It goes to a different issue, your Honor. We know in this correspondence the LabCorp admits they correlate—that they are correlating in Claim 18. And then all we're saying is if they understand the term "correlating" for Claim 18, there is this exact same quotation, correlating in Claim 13, so it's just a use of knowledge of what LabCorp understood. Goes to at least to willful infringement issue.

MR. HIGGINS: Your Honor, Claim 13 doesn't even have—doesn't have a correlating step in it and it doesn't—

MR. WHITEHAIR: That's what the second step is.

MR. HIGGINS: Claim 18 is one step claim. It doesn't have a correlating claim. And this letter was written before your Honor's interpretation of what Claim 13 meant.

THE COURT: Basically, what my ruling was is that you can't patent an idea. You have to patent an act or the test, and really that's about all my ruling was, so I'm not sure I understand what the—where you're going or what the problem is.

* * * *

[Page 881, line 22 to Page 883, line 4]

Q. What was your understanding of what was communicated very generally to LabCorp in that '99—July, '99 time frame?

A. The main thing it concerned was the very strong concern I had about the dangers to patients from adding this message. This is 165A, in which they told doctors not to use the single homocysteine for the diagnosis of B12 or folate deficiency. This was absolutely unbelievable to me. I realized that the vast, vast majority of doctors would look at this and say, "Huh? This is ridiculous." I mean if I have an elevated value for total homocysteine, I've already detected B12 and folate deficiency; and I think they would ignore it and go ahead and either treat the patient or do additional tests if they wanted to pin down which vitamin was deficient. But I think there would be a very small number, maybe no more than 1 percent, that would look at this and say, "Oh, I thought that if I got this as a risk factor for vascular disease or some hematologic problem—I thought that if it was elevated, this would help me diagnose B12 and folate deficiency. But I guess I must be mistaken." And so in those—you know, 1 percent is a small number; but if you're doing 50- or 100,000 tests a year, that means you're talking about 500 or a thousand times when a doctor is looking at this report trying to decide what to do. And in this small percent, if you're the patient, even one is a big number. The patients were being undiagnosed and not treated with the appropriate vitamin. We've already heard this week just how serious that can be. So that was the major issue that we raise the with our communication with LabCorp. We also pointed out that making somebody order a four-test panel and a second homocysteine when you already had the homocysteine we thought was—that wasn't medically dangerous but it was very unfair to patients, people that were going to pay for this, including insurance companies and the government.

* * * *

[Page 905, line 4 to Page 908, line 5]

Q. Did we discuss earlier today your contacts with Abbott?

A. Yes, we did.

Q. Do you have any documents relating to that?

A. Yes, I do.

Q. Let me turn—is it Exhibit 205 in the book—not the one we set down but the one before that.

A. Yes, it is.

Q. What is this document?

A. This is an article that was published by Dr. Shipchandler—Shipchandler, the individual that visited us, published in Clinical Chemistry and is about the fully automated measurement of plasma homocysteine with the Abbott IMX. That's their machine analyzer.

Q. When did you say it was published?

A. 1995.

Q. Is there a reference to your lab on the first page?

A. Yes, If you look on the right-hand side, under "materials," if you come down about six or seven pages "Clinical serum samples were provided by R.H. Allen of the University of Colorado." These were samples with elevated levels of total homocysteine from patients with B12 and folate deficiency.

Q. Is there another reference to Allen on the next page?

A. Yes. In the right-hand [illegible], if we come down till we get to something called [illegible]on parallelism," and if we just go back up three sides, it talks about gas chromatography mass spectrometry and it gives an equation, the correlation between 21 of our clinical samples and the Abbott assay.

Q. Is there a citation?

A. Yes, there is. It is No. 19.

Q. And where is that found?

A. It's found on the last page—well, there are two articles here. It's 81713. And in the right-hand column, three quarters of the way down, it's the Stabler et al. article. This is our article in which we describe our GC mass spec method for total homocysteine.

Q. And what's the—what's this article saying?

A. Well, I think the punch line of this article can be found if we go to the left-hand column, and in this paragraph that says, "We conclude," and come down about six lines.

Q. Let me ask you—excuse me.

A. Yeah.

Q. Is there a reference to the study?

A. Yes. I'm sorry. If we go back up a little bit. Let's go to the left-hand column of this page. Let's come down to where we're starting a new paragraph with "hyperhomocystinemia," and let's go to the second sentence: "In a recent study of 1100 elderly patients Selhub, et al., concluded that 29.3 percent of the cohort exhibited hyperhomocystinemia with 67 percent of this being associated with one or more manifestations of vitamin B deficiency." And the vitamins in this study were folate, B12, and B6. And then if we go on to the important conclusion of this paper, we're now into the next paragraph, about six lines down with, where it says: "The lowering of plasma homocysteine concentrations in hyperhomocystinemia by simple and inexpensive vitamin therapy may lead to intervention not only in elderly patients but also in the general population, with potentially concordant reductions in mortality and morbidity from cardiovascular diseases. An accurate, precise, and automated method for quantifying total homocysteine will help identify patients who might benefit from the intervention." Abbott knew from the very beginning, three years before they actually introduced this assay into the market, that this assay, as total homocysteine assays are - - are all about elevated homocys-

teine, deficiency we now know of B12 and folate, and their treatment for vascular disease and a whole lot of other conditions.

Q. Did Abbott prepare some materials for—I'm sorry.

A. I don't know if you want me to finish this exhibit. There is a second copy of this—

Q. Oh, I'm sorry. You're right?

A. —article. It starts with M81714. And the importance here—it's the same article we just went through. But if you look up in the upper right, there is a note that says, "Dr. Stabler, with compliments of the authors. Thank you for your help, Mohammad Shipchandler."

* * * *

[Page 937, line 1 to Page 938, line 7]

BY MR. WHITEHAIR:

Q. Doctor, do you have, based on what you described—Can you give us a review of the exhibit we've already looked at, Exhibit 165A, LabCorp report of apparent results?

A. Yes. I have this. This is a patient report that LabCorp started using in May of 1999.

Q. Would you read the section that you're going to refer to so that the record is clear.

A. Yes. And I might say that this report, to my knowledge, is still in existence today. It says, referring to the total homocysteine test: "This test is intended to be used as an independent risk factor for vascular disease and is not intended for the diagnosis of folate or vitamin B12 deficiency. LabCorp has available the megaloblastic anemia profile serum for that purpose."

Q. And what's your view of the accuracy of that statement?

A. Well, as I think we've learned, an elevated homocysteine is a marker for much more than vascular disease. It's a marker for B12 and folate deficiency, which in turn is related to Alzheimer's disease, birth defects, toxicity from anticancer drugs, the development of cancer. It's really—it's a marker—it's a risk factor for death from various manifestations of B12 and folate deficiency. And to indicate to physicians that it's only related to vascular disease, particularly not pointing out that the people at risk with vascular disease are the people that already have it, not people that don't, and to indicate—Again, most doctors won't be fooled; but even 1 percent or less of doctors, to fool them such that patients with elevated total homocysteines, which are clearly due to B12 and folate deficiency, I believe is very dangerous.

* * * *

Robert Allen—Cross

[Page 969, lines 3-6]

Q. And from May of '94 to July of '98, LabCorp performed that single homocysteine test using the GC mass spec method that's disclosed in the patent; correct?

A. That's correct.

* * * *

[Page 970, line 25 to Page 972, line 4]

Q. Now, you're aware in August of '98, LabCorp began performing the single homocysteine serum test using the Abbott method; correct?

A. That's correct.

Q. And that method doesn't use gas chromatography mass spectrometry, does it?

A. It does not.

Q. It's not covered by Claims 1 through 12 of the patent; correct?

A. That's correct.

Q. And you're aware that LabCorp continues to perform a single urine homocysteine test by GC mass spec; correct?

A. I'm aware of that, yes.

Q. And LabCorp continues to pay you royalties on that single test done by GC mass spec; correct?

A. Yes.

Q. And LabCorp continues to perform the four-panel metabolite test, which we looked at a report up here for, by GC mass spec; correct?

A. Yes.

Q. And they continue to pay you royalties for that test?

A. That's correct.

Q. And that's the test that—the GC mass spec test or the test that LabCorp uses some of your software that—or technical know-how that you gave them early in the relationship; correct?

A. That's correct.

Q. And they don't use that—that software or robot to perform the Abbott test, do they?

A. I don't believe so.

* * * *

[Page 977, line 4 to Page 982, line 1]

Q. Dr. Allen, is it Metabolite's position that Metabolite is entitled to a royalty on every single homocysteine assay where the result of the assay is less than 13.9?

A. Well, it's Metabolite's position that virtually with a few incredibly rare exceptions that virtually every total homocysteine test that's done in the United States today is

for the purpose of detecting a deficiency of B12 or folate and that as Judge Weinshienk has defined correlating, there are two parts to it. It means to establish a reciprocal or a mutual relationship. And every time a total homocysteine is done, again, with these few very rare exceptions, the physician then either establishes in the physician's mind that there is a mutual relationship between an elevated level and a deficiency of cobalamin or folate, or that there is this reciprocal relationship between an unelevated value and the absence of cobalamin or folate deficiency.

Q. Trudy, put up Claim 13 again, please.

Where in that claim does it say unelevated value and absence of a deficiency?

A. That's what "correlating" means. There is no laboratory test that either an elevated level or a low level, only then do you get information. Every laboratory test, abnormal results give you information and normal results give you information. That's the meaning of what "correlating" means. It's this mutual relationship, and it's a reciprocal relationship.

Q. Dr. Allen, read the second step of Claim 13.

A. "Correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate."

Q. You didn't say correlate an unelevated level with an absence of a deficiency of cobalamin or folate—" did it?

A. It says "correlating." And as I understand it, Judge Weinshienk has stated what "correlating" means. And that means—I may be off a touch on the language, but I think her ruling was it means to establish a reciprocal or a mutual relationship. And that's exactly what correlating means in medical practice.

Q. Dr. Allen, the only term relating to elevated or unelevated in that claim is elevated; correct?

A. The word "correlating," correlating an elevated level; and that means just what I I've testified it means.

Q. It means you have to have an elevated level to correlate, does it not?

A. No, it does not. That's not what correlating means. It means to establish a mutual or a reciprocal relationship. I've never heard of a situation where anyone said that a test was only useful and provided information when it was high or low.

Q. Dr. Allen, you understand that the Court also said that the—strike that.

The Court said that correlating meant to establish a mutual or reciprocal relationship with a deficiency of cobalamin or folate; correct?

A. That sounds familiar. If we're going to get real precise, probably would be helpful to show me exactly the words that Judge Weinshienk used.

Q. Well, do you understand that—

THE COURT: We may need the order, because I can't remember the exact wording. It was a long time ago.

I'm not sure you really need [t]o go into this. When the jury gets instructions on the law, this will be explained to them, unless you need to ask him the question.

MR. HIGGINS: Well, I can move on then, your Honor.

THE COURT: Go ahead.

BY MR. HIGGINS:

Q. Let me ask you, Dr. Allen: Do you understand that the second step involves a discrete sequential step from the first assaying step? You understand that from the Court's order?

A. I understand from the order that it's a, you know, a different step and you can't do it at the same time, yes.

Q. Now, what act falls within the second step? What does a person have to do to fall within the second step of Claim 13?

A. Well, I think—

MR. WHITEHAIR: Objection to the extent it's calling for a legal conclusion.

THE COURT: All right. Of course, he can't answer as a legal conclusion. He can state his understanding, however.

MR. WHITEHAIR: Thank you.

THE COURT: If that's what you're asking.

MR. HIGGINS: Yes, your Honor. I'm trying to find out what someone has to do to infringe. That's the purpose of the claim.

THE COURT: Go ahead. Ask your question.

BY MR. HIGGINS:

Q. Dr. Allen, what does a person have to do to fall within the second step of Claim 13, your understanding as a physician and the inventor?

A. Well, as I understand Judge Weinshienk's ruling, a physician establishes a reciprocal or mutual relationship. Again, I'm struggling to remember the exact language of her claim [sic], but I understand that's what we're using in this case.

Q. Well, what specific act does the physician do to establish that mutual or reciprocal relationship?

A. The physician takes the value that's been determined by the assay and then based on everything the physician knows about that patient, he or she establishes a mutual relationship between an elevated value if the patient—if the

physician thinks the value is elevated for an individual patient and a deficiency of cobalamin or folate, or if the physician believes that for that particular patient the value is not elevated, then that physician in their mind establishes that there is not a deficiency of cobalamin or folate.

Q. And it's all done in the mind?

A. I think so, yes.

Q. And again, where in Claim 13 does it [say] establish that there is not a deficiency of cobalamin or folate?

A. That is the meaning of the word "correlate."

Q. That's Dr. Allen's meaning of the word "correlate"?

A. No, that is Judge Weinshienk's meaning, and it's the meaning of physicians throughout the United States. That's how we interpret laboratory tests.

Q. So it's your testimony that the discrete step of Claim 2 is the mental process in a physician's mind?

MR. WHITEHAIR: Objection to the extent that calls for a legal conclusion.

THE COURT: The objection is overruled. He may answer based on his understanding, not a legal conclusion.

THE WITNESS: Well, I think that's true. I guess as we're talking the question is could someone establish that in writing someplace? I suppose. I don't know whether that would be correlating or teaching correlating; but certainly as physicians practice medicine, this is a step that takes—that is performed by the physician in the physician's mind. Other people might be able to do the same thing.

* * * *

[Page 982, line 15 to Page 983, line 20]

Q. And you recall that initially you filed a Claim 13 to cover an assay for any elevated level of total homocysteine; correct?

A. That is not correct.

Q. Trudy, put up Exhibit MB. And if you would, blow up the top part of it, the first claim. Dr. Allen, if you would, read Claim 13 as originally filed and rejected that's shown on Exhibit MB.

A. Yes. "A method for detecting a deficiency of cobalamin or folate in warm-blooded animals by: assaying body fluids for the presence of elevated levels of total homocysteine."

Q. And in response to that—that claim as filed, the examiner rejected it, saying that the preamble was just a statement of intended use. Do you recall that?

A. I recall that that's how the examiner interpreted that statement. That was perfectly proper for the examiner; but as I testified earlier, our intent was clearly to limit this claim for detecting a deficiency of cobalamin or folate. And if we weren't going to limit it to that, that wouldn't even have been put in there. We would have just said Claim 13, assaying body fluids for elevated levels of total homocysteine. We didn't put that in. We clearly put what we thought was a limitation.

Q. So you agree that Claim 13 doesn't cover a method of monitoring and screening for risk of heart disease by assaying serum total homocysteine; correct?

A. I do not agree with that. I think that is absolutely false, because it's cobalamin and folate deficiency that's responsible for the risk and for the vascular events and that doctors in this country know that. And when they order this test for a patient with vascular disease, they're trying to find out if the patient is cobalamin or folate deficient so they can treat patients for those deficiencies.

* * * *

Dr. Kilmer McCully—Voir Dire

[Page 1025, lines 12-16]

Q. Are you an expert in B12 and folate?

A. I would not say so. I would say I have a knowledge of this area, but this has not been my primary field of concentration. My primary field of research has been homocysteine and vascular disease.

* * * *

[Page 1026, lines 14-17]

THE COURT: At this time, the Court is satisfied that Dr. McCully may be helpful to the Court and Jury and will accept him as an expert or opinion witness in the science and medicine of homocysteine.

* * * *

Dr. Kilmer McCully—Direct

[Page 1063, line 16 to Page 1067, line 17]

Q. And can you quantify how many elevated levels of homocysteine in the general population would be attributable to renal disease or B6 deficiency or these other causes or B12 deficiency or folate deficiency?

A. This question has not been examined in detail. The one study that comes to mind that has tried to answer this question is the Framingham heart study, in which they analyze the dietary intake of these three B vitamins, related them to the plasma levels and also the level of homocysteine. And what they found was that in a group of elderly participants—these are individuals between the age of 65 and 93—that approximately a third had no evidence of vitamin deficiencies or elevation of the hornocysteine; but about two-thirds of this group had some evidence of deficiency of one

of these three B vitamins. And when deficiency was present, they found an elevated level of homocysteine.

We know that renal disease is very common in this age group, also; and so I've estimated that perhaps as much as—perhaps as much as 50 percent of the individuals with elevated homocysteine may have some other cause than dietary deficiency.

Q. So if all the renal disease and hypothyroidism and these other factors that you mentioned—they account for approximately half of the elevated levels of total homocysteine, in your opinion?

A. As much as that. It's difficult to be certain of the exact figure, but a significant fraction will have these other causes.

Q. Now, do you have recommendations--do you have a recommendation for what someone should do if their homocysteine is elevated?

A. Yes. As explained in my earlier articles and also my recent books, I believe that the first line of therapy should be dietary improvement. And this is in my opinion an extremely important way to improve and preserve health; that one of the benefits of improving the diet will be to lower homocysteine levels. And the reason of this—for this is manyfold. First of all, an optimal diet, such as my heart revolution diet, recommends eating fresh vegetables, fresh fruits, fresh seafood, meats, whole grains, and so forth, to provide in the food an optimal level of all micronutrients, including the three vitamins that we've been discussing.

But such things as antioxidants and fiber and vitamins, like fat-soluble vitamins, are all important to good health. And by improving the overall diet, this is the best way in my opinion to preserve health and prevent vascular disease. And I've been a consistent advocate of this for many years.

In the case where dietary improvement has been carried out for some months or years and one still observes elevated homocysteine levels, I think there is a case for adding supplemental B vitamins to help control the level of homocysteine with the hope of preventing vascular disease.

Q. And when you say supplemental B vitamins, which B vitamins are you referring to?

A. Well, the three B vitamins that control homocysteine levels are B6, B12, and folic acid. These are the three that I emphasize because of their direct controlling function in the level of homocysteine.

And in my recent book, I give a table in which I relate the levels of homocysteine and the risk of vascular disease to the recommended intake of the supplemental vitamins in addition to dietary improvement.

Q. And Trudy, if you'd put up Exhibit BE.

Dr. McCully, do you recall this Wilcken article dated 1981?

A. BE?

Q. BE. Do you recall we discussed—

A. Yes, I do.

Q. —before the break and—

A. I have it.

Q. —and there was a Figure 2 in that article.

Now, does that article support your position or opinion that supplemental B12, folate, or B6 will lower homocysteine?

A. Yes.

Q. And when you first were involved in this field, what B vitamin did you focus on in the beginning?

A. I focused primarily on vitamin B6. The reason for that was that the important studies of Rinehart in B6-deficient monkeys were a direct—directly related homocystine to arteriosclerosis, in my view.

In addition to that, the patients—most of the patients, or many of the patients with homocystinuria respond to vitamin B6 therapy. About half of the most common form of patients with homocystinuria respond to B6 therapy by lowering of the homocystine level and also improvement in development, prevention of disease, and prevention of vascular disease.

So—and other reports that I found in the literature relating B6 deficiency to vascular disease—these were the reasons that I focused on the relation between homocystine and vitamin B6 in my earlier studies.

Somewhat later, other investigators, some of whom we've discussed today, began to focus more closely on folic acid and vitamin B12.

In fact, when I was first investigating this—this theory in 1968, I examined a series of cases from our files at Massachusetts General Hospital of cases of pernicious anemia, of patients who had died before liver therapy was introduced in the 1920's. Unfortunately, I was not able to document any evidence of vascular disease in these patients, so I left it to other investigators to explore this area, which I felt was important but was beyond my capability at that time.

* * * *

Dr. Kilmer McCully—Cross

[Page 1068, lines 4-24]

Q. Total homocysteine, homocystine, homocysteine—they sound similar, don't they?

A. Yes.

Q. They're not the same, are they?

A. No. It's confusing, I know.

Q. Homocystine, in fact, is one of the several species that make up total homocysteine; correct?

A. Correct.

Q. Okay. As you went through the many exhibits and many articles shown to you by Mr. Higgins this morning in the fat notebook, did you find a single one that measured total homocysteine in a B12 or folate-deficient patient?

A. The disulfide, you're referring to?

Q. No, I'm referring to total homocysteine.

A. Okay.

Q. The collective species, all of them together.

A. Did I find them in here? I mean—

Q. Did you find anywhere in the notebook of articles an article before 1986 that measured total homocysteine in a B12-or folate-deficient patient?

A. I don't believe so, no.

* * * *

[Page 1083, line 22 to Page 1084, line 9]

Q. That's in fact exactly what you did on yourself, isn't it? You had a—a total homocysteine test done on yourself?

A. Yes.

Q. And not MMA test?

A. No.

Q. And you found that the level was something higher than you would like it to be?

A. Yes.

Q. So you took both vitamins?

A. Well, I went on a large-scale program of dietary improvement and—

Q. And that includes the ingestion of more B12 and folate?

A. But I also took multivitamins, yes.

* * * *

[Page 1085, line 7 to Page 1086, line 2]

Q. In your books, do you recommend that the reader have his MMA checked?

A. No.

Q. But you do recommend that he have his total homocysteine checked?

A. Yes.

Q. And if the reader finds that his total homocysteine is high, you recommend that he ingest more B12 and folate; right?

A. Well, I recommend that he be evaluated by a physician to determine the cause of his elevated homocysteine. A thorough history, physical examination, thorough evaluation by a competent physician to determine the source of the elevated homocysteine. That's the first step. The second step, I recommend dietary improvement. And I have a series of chapters and plans for how this can be done to eat The Heart Revolution diet. And then I say in the book that if—if there is no other cause for the elevation of the homocysteine and if dietary improvement does not succeed in lowering it to an optimal level, then I suggest that the patient should consider taking supplemental vitamins, including folate and B12.

* * * *

[Page 1096, line 15 to Page 1100, line 10]

Q. Do you recognize this as the LabCorp Directory of Services that we discussed before the lunch break?

A. Yes.

Q. Could you please turn again to the same page we were on before, which is labeled L324 in the bottom right-hand corner. Do you see in the left-hand column the same test that we focused on before, test 706994 for homocysteine, plasma or serum?

A. Yes.

Q. Do you see the heading "related information"?

A. Yes.

Q. And do you see the reference to "anemia profile megaloblastic, serum"?

A. Yes.

Q. You would not have been aware of this cross-reference in this test at the time you signed your report because you had not been furnished this Directory of Services; correct?

A. That's correct.

Q. Look on down, if you would, please, to the heading "use" about three quarters of the way through that test and just about midway on the page in the left-hand column. Do you see it?

A. Yes.

Q. Do you see the sentence, "Evaluate borderline folate deficiency as part of anemia profile megaloblastic, serum test"?

A. Yes.

Q. Do you interpret that statement to mean that the use of this test is to evaluate borderline folate deficiency along with another test?

A. Yes. I assume there are other tests in the anemia profile and that this is part of it.

Q. Do you see the heading "references," which is the last heading under the description of this test in the Directory of Services?

A. Yes.

Q. Do any of the articles that are under the heading "references" describe to the reader the correlation between elevated homocysteine and B12 or folate deficiencies?

A. Could you repeat the question?

Q. Do any of the articles listed under the heading "references" in the description of this test describe to the reader the correlation between elevated total homocysteine and B12 or folate deficiencies? If it would be helpful to review the articles, I can make them available to you.

A. I believe the Ueland article in Clinical Chemistry addresses this question, as I recall. I'd have to review it to be certain.

Q. Could I ask you to look at a copy of the Ueland article in Plaintiff's Exhibit 185 so that you could determine that.

A. Yes.

Q. Okay. Ueland does teach to the reader the correlation between elevated homocysteine and B12 and folate deficiencies?

A. Yes.

Q. And that's one of the several articles listed under "references" in the description of the test. What about the Malinow article? Do you see that under the heading "references"? And if it would help you in answering my question, which I would anticipate will be the same, you might look at Exhibit 188. While you're looking at that, just to be clear for the record, the question again is: Does the Malinow article describe to the reader the connection between total homocysteine and B12 or folate deficiencies.

A. The article focuses on arterio-occlusive diseases, and the discussion of the concentrations of the homocysteine refer to the correction by folic acid with pyridoxine, vitamin B12, choline or betaine.

Q. Is the answer to my question no, then?

A. It doesn't address the—the article doesn't address your question directly. It does indirectly.

Q. What do you mean by indirectly?

A. It discusses, as mentioned in the summary, that the increased homocysteine concentrations associated with coronary disease can be corrected by folic acid, pyridoxine, B12, choline, or betaine therapy.

Q. So it does teach that elevated levels of total homocysteine –

A. Yes.

Q. —are correctable with B12 and folate?

A. Yes.

Q. Okay. What about the Robinson article, which is also listed under the heading "references"?

A. Which one is that?

Q. That is Plaintiff's Exhibit 187.

A. Yes, it does address the—the answer to your question is yes.

Q. What about the Verhoef article, also listed under the heading "references"?

A. Which one is that?

Q. Plaintiff's Exhibit 186.

A. Yes. This addresses the question of vitamin deficiency in relation to elevated homocysteine levels.

Q. Thank you.

* * * *

[Page 1103, line 21 to Page 1105, line 8]

Q. Back to the form of patient report, which is Exhibit 165A. Do you see in the right-hand column about a third of the way down a paragraph beginning with "this test"?

A. Yes.

Q. And it goes on to state: "This test is intended to be used as an independent risk factor for vascular disease and is not intended for the diagnosis of folate or vitamin B12 deficiency." Is that how you read it?

A. Yes.

Q. Now, if a patient does have elevated total homocysteine, you say in your books that's a bad thing, don't you?

A. Yes.

Q. And elevated total homocysteine is indicative of a need for additional B12 or folate, is it not?

A. It can be.

Q. So if a patient has elevated total homocysteine, shouldn't something be done about that?

A. Yes.

Q. You testified before lunch, I believe, that armed with a patient report only, showing an elevated level of total homocysteine, a physician can't tell for sure that the patient is deficient in B12 or folate. Have I paraphrased you well?

A. That's correct.

Q. But armed with a patient report showing elevated total homocysteine, the physician will know that it's more probable that the patient is B12 or folate-deficient than if the—if the physician is not armed with that report. Isn't that fair to say?

A. Yes.

Q. So it's a matter of probabilities; right?

A. Yes.

Q. Isn't that what it means to correlate? It's not a matter of certainty, is it? It's a matter of probabilities.

A. To correlate is to—is to relate one finding to another.

Q. But not necessarily with certainty but only with probabilities?

A. Not necessarily—that's correct.

* * * *

[Page 1110, line 15 to Page 1111, line 20]

Q. Let me ask you to consider a hypothetical question, if I may, since you've been qualified as an expert for a limited purpose. Let's assume for a minute that your theory is right. It hasn't been proven, but let's assume that for the purposes of argument elevated total homocysteine indeed causes vascular disease; okay? And let's assume further for purposes of argument that your theory is not only right but some physicians believe it is right. And so some physicians indeed order total homocysteine tests for their patients in order to assess their risk for vascular disease. Okay? You're with me in my set of assumptions?

A. Yes.

Q. If all that's true and a total homocysteine test for the physician's patient comes back elevated, then the physician should conclude, according to your theory, that the patient has a heightened risk for vascular disease; am I right?

A. That's correct.

Q. Because a heightened risk for vascular disease in an effect of elevated total homocysteine, you theorize?

A. That's correct.

Q. Well, even assuming that all that were true, that doesn't address the treatment side of the equation, does it?

A. That's correct.

Q. Shouldn't the physician in those circumstances also be concerned about the treatment for this elevated total homocysteine?

A. Yes.

Q. And in your professional experience, physicians indeed normally are concerned about the treatment - -

A. Yes.

Q. —of conditions.

* * * *

[Page 1111, line 21 to Page 1113, line 9]

Q. Dr. McCully, could you look at Defendant's Exhibit A, please.

A. Oh, yes.

Q. Do you recognize this as the patent at issue in this case?

A. Yes.

Q. And you've reviewed it in the past; correct?

A. Yes.

Q. You're not an expert in interpreting patent claims, are you?

A. No, I'm not.

Q. Leave aside the claims, then. Okay? Apart from the claims, is the language of the patent misleading or inaccurate or untrue in any respect?

A. No. In general, no. There are a few minor typographical errors that I picked up; but aside from that, there are no—no major errors that I found in my reading of it.

Q. These two University of Colorado professors, Dr. Allen and Dr. Stabler, named as inventors of the patent truly are experts in B12 and folate, are they not?

A. Yes.

Q. And Dr. Lindenbaum, the late Columbia professor, was an expert in B12 and folate; won't you agree?

A. Yes.

Q. They've received a lot of recognition for their work, haven't they?

A. Yes.

Q. They've had over a hundred articles published in leading scientific journals?

A. I don't know how many, but I know that there are multiple articles.

Q. They haven't gotten their names in the paper about this, but they've received a lot off recognition from their peers in the field, wouldn't you say?

A. I would say hematologists, yes, have used their findings and to benefit their patients, yes.

Q. Now, the idea that elevated total homocysteine can be brought to save levels by administering B12 and folate is a pretty significant idea, wouldn't you say?

A. It's an important idea, yes.

* * * *

Robert Allen—Cross

[Page 1133, line 17 to Page 1137, line 11]

Q. So you run into situations where someone may read something in a newspaper or magazine or see it on television about a medical test and next time they go to the doctor they ask for it?

A. Well, I would say they bring it to the attention of the doctor and ask questions.

Q. Now, assume a person were to read about homocysteine and the risk of heart disease and goes to their physician

and asks the physician to measure their total homocysteine. Assume that. And assume the level comes back at a 5 and nothing is done. The doctor says, ["]You got a 5."

Now, did the doctor infringe Claim 13 of the patent, in your opinion? Is it Metabolite's position that the doctor infringed Claim 13?

A. Well, I think that's covered by Claim 13, because I think doctors in this country, when they order a total homocysteine, whether it's risk factor for vascular disease or other causes, when the result comes back, they then establish whether there is a mutual relationship between an elevated level and a deficiency of cobalamin or folate, or whether the reciprocal relationship is present[]; namely, the value is not elevated and there is no deficiency. That's the way Judge Weinshienk has defined the word "correlate," and I think physicians do that. And I think a physician that looked at a value of 5 would—would very, very, very likely decide that there was a reciprocal relationship in this particular patient between a non-elevated level and an absence of cobalamin or folate deficiency.

Q. What discrete sequential step did the doctor perform that falls within Claim 13?

A. The step I just explained. He did the correlate step.

Q. And what exactly did the doctor do?

A. Well, I think I just answered that. The doctor looked at the value of 5, and I think it's extremely likely with a value of 5, if there was no other information present, no prior values, the doctor would have established that there was a reciprocal relationship between this almost certainly or incredibly likely non-elevated value and an absence of cobalamin or folate deficiency.

Q. Trudy, put up Exhibit 26.

Dr. Allen, read—now, this is the claim chart that the plaintiffs have prepared for this litigation; correct?

A. That's correct.

Q. If you would, read the last sentence or—strike that—the last phrase after "and."

A. "To establish a mutual or reciprocal relationship between a level of total homocysteine raised above the normal range in said body fluid with a shortage of cobalamin or folate necessary to health."

Q. Now, the 5 in my hypothetical is not raised above the normal range, according to your patent, is it?

A. I think we went through this the last time I was on the stand. A 5, it is incredibly unlikely that that is elevated above the normal range.

Q. And the second step requires a correlation of an elevated level with a deficiency; correct?

A. Well, it says, as Judge Weinshienk has defined the word "correlate," it means, quote, "to establish a mutual or reciprocal relationship between a level of total homocysteine raised above the normal range in said body fluid with a shortage of cobalamin or folate necessary to health."

Q. And the 5 is not raised above a normal range; correct?

A. It is possible, but it is extremely unlikely.

Q. And for any particular result of a single homocysteine test that's—well, strike that.

Well, let me ask you: Does the patient in my hypothetical—did the patient—what the patient did fall within Claim 13?

A. You mean asking the physician to consider ordering a total homocysteine test?

Q. Yes.

A. I don't think just asking for a total homocysteine test, that act all by itself—I don't think it does.

Q. What about receiving a result from the physician—asking and receiving a result from the physician? Is it Metabolite's position that that would infringe Claim 13?

A. Well, I suppose—I think it's very unlikely that a patient would get a test and the doctor would just give them the result, but I think patients that would go to the doctor and ask for a total homocysteine are very likely to have an understanding of what the result might mean.

Q. So is it Metabolite's position and CTI's position, to your knowledge, that a patient asking a physician to perform total homocysteine test and receiving the result would infringe Claim 13?

A. Well, I—we have LabCorp doing the test, the physician ordering the test. Somebody, whether it's the physician or the patient, is going to understand how to interpret the test and will perform the correlating step. So somebody will be infringing Claim 13.

And as we've talked about, there are different kinds of infringement. There is inducing and contributory; so in that situation, I think LabCorp would be guilty of contributory, and the physician or the patient would be part of that.

* * * *

Dr. Robert Allen—Redirect

[Page 1225, line 8 to Page 1228, line 8]

Q. Do you recall discussing the issue of total homocysteine as a risk factor?

A. Yes, I do.

Q. What do you understand the argument to be about its use as a risk factor?

A. I think that that argument goes that a doctor will order a total homocysteine on a patient in order to see if that patient is at risk or has an increased chance of developing vascular disease; that once that result is obtained, if it's

elevated, the doctor does nothing more than inform the patient that here's some bad news for you, you're at higher risk for vascular disease than I thought you were before I got the test and, you know—

Q. What, in fact, do doctors do after receiving information on this test?

A. Well, doctors—

MR. HIGGINS: Objection, your Honor. Limited to his knowledge.

THE COURT: All right. Would you restate your question. You're asking him to the best of his knowledge.

BY MR. WHITEHAIR:

Q. To your knowledge—to the best of your knowledge, Doctor, what do doctors--pardon me. To the best of your knowledge, what do doctors do when they receive the test results on a single total homocysteine in a situation where someone considers it a risk factor?

A. Well, they may or may not do additional tests; but in virtually every case, they then end up treating the patient with either cobalamin and/or folate.

Q. Where do doctors learn about that step?

A. Well, they learn about it in textbooks, they learn about it in multiple journal articles, they learn about it from LabCorp in the articles that are listed in the Directory of Services, and they also learn it from articles, continuing medical education articles that Dr. Wentz has written.

Q. Do you recall having it suggested to you that no royalty should be paid if there is a normal result?

A. I have heard statements made that the patent only covers tests where the results come back as elevated, yes.

Q. What is your reaction to that, Dr. Allen?

A. Well, I don't know of any medical test where the information is useful only if it's elevated or low or abnormal.

In every test that I know of, information that the doctor acts on is always obtained regardless of the normality or abnormality of the test result.

Q. And what's the analogy that you use in your practice?

A. Well, the analogy that I touched on in my earlier testimony was a pregnancy test. If the pregnancy test comes back as positive, then the doctor correlates. We always correlate with any test result. In this case, the doctor would establish that there is—would know that there is a mutual relationship between a positive pregnancy test and a woman being pregnant and then would obviously act on that to make sure the patient received care throughout pregnancy and afterwards.

Q. And what about the opposite result?

A. Well, if the pregnancy test is negative, then that's the reciprocal. A negative test indicates no pregnancy, and the doctor would act on that. It would make a difference whether the patient wanted to be pregnant or not. If the patient did want to be pregnant and the patient had been trying for a long time, there might be various fertility treatments or things that might be done. If the patient did not want to be pregnant, then the doctor might inform the patient about various birth control options.

Q. Is this analogy you're describing applicable to the total homocysteine only test?

A. Yes. I think it's applicable to every test. Doctors, when they order the total homocysteine test and when it comes back, as I've testified repeatedly, they always correlate. If it's elevated, it's the mutual relationship with cobalamin or folate deficiency. If it's not elevated, it's the reciprocal or absence of cobalamin or folate deficiency. They act accordingly with each result, depending on the patient—

Q. I'm sorry.

A. I was just going to say depending on the individual patient.

* * * *

Peter Wentz—Direct

[Page 1244, line 10 to Page 1245, line 9]

Q. Let's talk about your role in the LabCorp Directory of Services, if we may. What is the Directory of Services?

A. The Directory of Services is a publication produced by Lexi-Comp. It includes tests that are published tests that are provided by LabCorp to our clients, so it's a listing of those tests.

Q. So it's a listing and description of the tests that LabCorp makes available to its customers?

A. Yes.

Q. Does it come in book form?

A. Soft copy. There is a few hard copies, but most of them are soft copy, hard copy.

Q. Something I could pick up in my hands; right?

A. Yes.

Q. But a pretty big thing that I'd pick up in my hands; right?

A. Fairly thick.

Q. Like a phone book?

A. A local phone book.

Q. It's also accessible on line, is it not?

A. The—yes. We have an on line Directory of Services.

Q. Is the Directory of Services a tool that LabCorp uses to market its tests to physicians?

A. Is it a tool? Used for marketing? There may be some promotional advantage of having it on line. Certainly, we use that tool to educate our physicians and clients.

* * * *

[Page 1314, line 22 to Page 1316, line 1]

Q. Let's go to the patent, if we could. I believe there is copy of it in Defendant's Exhibit A.

A. Thank you.

Q. If you'll look to the second to last page, Claim 13. Now, as you indicated in your e-mail to the Mayo Clinic, Claim 13 covers a procedure in which both the following steps are performed; right? (1) an assay step and (2) a correlating step?

A. I believe that was the gist of my e-mail.

Q. And it doesn't matter whether the test is by GCMS. Correct?

A. I believe that was in my e-mail, yes.

* * * *

[Page 1315, line 9 to Page 1316, line 8]

Q. Now, do you understand the word "correlating" to mean establishing a mutual or reciprocal relationship?

A. Yes. That's been defined by the—

MR. JABLONSKI: I would object to the question, your Honor. The Court has defined what correlating is, and there is no reason for Mr. Wentz to redefine it for the jury.

THE COURT: He may state his understanding. The objection is overruled. Not a legal definition but his understanding.

BY MR. BEATON:

Q. And you've had that understanding all along, haven't you, as to what correlating means?

A. Well, it was defined by the Court. I do have that appreciation, yes.

Q. Was it defined by the Court in a manner different than your understanding?

A. I—I don't recall if it was different necessarily. It was a definition.

Q. Now, LabCorp still does pay royalties on the panel test; right?

A. That's correct.

Q. And LabCorp pays royalties on the panel test still regardless of whether the result is high, low, or in between; right?

A. Irregardless [sic]. That's correct.

* * * *

Peter Wentz—Cross

[Page 1316, line 16 to Page 1317, line 17]

Q. LabCorp does perform the assay step in the panel test; right?

A. Yes.

Q. Is it your position that LabCorp does not perform the correlating step in the panel test?

A. Quite emphatically it does not perform the correlating step. That's a—that's a separate, distinct step that's performed by the physician who receives the—our results.

Q. Could you look at your deposition from January, 2000, page 122.

A. Yes.

Q. Line 24.

"Question: Right. And 706960 falls within the claims of the licensed patent because it includes a correlating

step. That's my question." Before I go on to the answer, 706960 is the panel test; correct, Doctor?

A. I'm sorry. What was your question?

Q. 706960 is the panel test; right?

A. Yes, that's the four-panel test.

Q. Let me start again then. "Question: Right. And 706960 falls within the claims of the licensed patent because it includes the correlating step. That's my question." "Answer: Yes." Did I read it right?

A. Yes, you did.

* * * *

[Page 1418, line 3 to Page 1420, line 13]

Q. All right. I would like to turn now to the—switch to the Abbott test. You remember you were questioned about that by Mr. Beaton, and I want to ask you some additional questions about that. When is it that you at LabCorp first became aware that there was even going to be an Abbott test?

A. It was the same publication that Dr. Allen cited by Shipchandler in 1995 that was an Abbott publication. It appeared in the Journal of Clinical Chemistry. That's my—

Q. What is your recollection of what that said?

A. Well, it described the Abbott method. Basically the same Abbott method that's in use today.

Q. Was the Abbott method commercially available in 1995?

A. Unfortunately not.

Q. When, to your knowledge, did it first become available?

A. Reagents became available, I believe, in the latter part of 1997.

Q. Does a test or kit of the kind that Abbott was proposing to sell require approval by the FDA?

A. Yes. All diagnostic kits must be FDA approved.

Q. What is your best recollection when this diagnostic kit became FDA approved?

A. I think we received a letter in October of 1998 that it had been FDA approved.

Q. And what did that permit LabCorp to do?

A. Well, it permitted us to switch over from bulk reagents, which we were using, to the kit reagents.

Q. You have testified in response to questions by Mr. Beaton that the determination to go forward with the Abbott test was made in August of 1998; is that correct?

A. Well, that's when we implemented it. The determination had been made prior to that.

Q. Approximately when was the determination itself made?

A. It would have been made after we finished our evaluation of the bulk reagents.

Q. Did you participate in that evaluation?

A. Yes.

Q. Tell us briefly what you did.

A. Well, I had to obtain an import license, USDA import license. I had to apply for that because these bulk reagents were coming from Oslo, Norway, from a company known as Axis, A-X-I-S, Chemicals. So I had to go through the whole process of applying for the import license and then—and that took probably four to six weeks. And then once that occurred, then I could place an order for the bulk reagents.

Q. And how did you use those bulk reagents?

A. Well, we used it in an evaluation of the procedure. We had by that time an agreement with Abbott so that they had set up a research, what they called, I think, a research-type instrument in our laboratory.

Q. Was that done pursuant to an agreement with Abbott?

A. Yes.

Q. Okay. And what were you doing during this research phase?

A. Well, we were going through a method evaluation.

Q. And what was your evaluation? How did you like it?

A. Well, the results of the evaluation were that we had accepted it. We accepted that particular procedure.

Q. What were you looking for?

A. Well, we were looking for a method that was at that time faster, more cost-effective, had excellent precision, reproducibility; that is, from not only within a run but from day to day and one that gave good results.

* * * *

[Page 1421, line 6 to Page 1423, line 3]

Q. Who participated in this research or evaluation phase other than yourself?

A. Well, individuals within our laboratory under my direct supervision—of supervisors, techs, chemists.

Q. And what were your conclusions at the end of this period?

A. Well, the conclusion was that we had a good method, the Abbott procedure was acceptable; and we placed it into operation in August of 1998.

Q. What did you see as the advantages?

A. Well, as I mentioned, the big advantage was, I think, reduction in the turnaround time. A procedure that for the single homocysteine that took, oh, upwards of 18 hours to turn out a result now was reduced to a matter of minutes. So as far as throughput, you know, putting samples through the instrument and generating results, the Abbott procedure was far superior to the procedure that we were using.

Q. And what was the procedure that you had been using?

A. That was the GCMS procedure.

Q. And was that the licensed procedure under the agreement with the plaintiffs in this lawsuit?

A. That's correct.

Q. Now, what is the difference between the kit and the bulk reagent?

A. Well, in size, primarily. The kit [sic], I believe, consisted of components, and you had to put the components together, whereas the kit, everything was together. There was no mixing up of reagents. Everything was premixed. All you had to do was place these reagents directly on the instrument, which was the Abbott. There was no preparation involved.

Q. That is a benefit?

A. That's always a benefit. I mean it takes time to prepare reagents. And the Abbott procedure virtually eliminated that phase of it.

Q. Is that procedure helpful in eliminating human error?

A. Well, anytime you can reduce the number of steps in a procedure, you reduce the opportunity for error.

Q. Was it important to LabCorp during this period in 1998 that it be able to speed up its accomplishment of these tests?

A. Yes.

Q. And why was that?

A. Well, I like to use the term critical mass. We had reached critical mass when it came to our single homocysteine testing.

From a period of January of 1997 through December of '97, we had—we had had a 300 percent increase in our homocysteine requests. We went from a thousand a month to 4,000 a month.

On into '98, that number just seemed to skyrocket. We couldn't keep up with the work using GCMS.

* * * *

[Page 1426, line 17 to Page 1429, line 2]

Q. Dr. Wentz, how do you know that in 1997 and 1998 there was a significant increase in the requests for the single homocysteine test?

A. Well, people told me, for one thing, they were having a hard time keeping up with the workload. Plus the numbers were reflected in that report, that workload report I just mentioned, the HLR tot. It's showed basically an exponential increase in the number of requests we had received for the single homocysteine in that time period.

Q. Did that burden you and your technicians at the division where this was being done?

A. That's putting it mildly, yes.

Q. And did you kind of welcome the commercial availability of the Abbott test as a way to deal with that problem?

A. Well, it was an advance in the technology, yes.

Q. Why would you describe it as an advance in the technology?

A. Well, it virtually eliminated all the prep time required to get a sample ready for GCMS.

Q. Is the Abbott procedure essentially automated?

A. Yes.

Q. Now, you were asked some questions about whether you were expert in various and sundry disciplines, and you responded to those. And I want to just return to this matter of homocysteine, if I could.

What did you do after you were assigned or became responsible for the performance of the four-test panel pursuant to the licensing agreement with the plaintiffs to inform yourself about homocysteine?

A. Well, I tried to get all of the materials that I could from the literature. It was a little bit difficult in—I think the early 90's. It wasn't until when I got on line with the national Library of Congress that I could get reports, get directly from Duke University that I was able to get the information that I needed, plus Dr. Allen was—shared a lot of that information with me as well.

Q. Did you by those methods, your own reading and discussions with Dr. Allen, become informed about homocysteine?

A. Yes. I made it a point to become informed.

Q. Now, you have said that you are not expert in homocysteine. That's right, isn't it?

A. I did state that. That's correct.

Q. Okay. And you have not, for example, like Dr. McCully or like Dr. Allen or like Dr. Stabler, you know, sought any grants or conducted any independent research with respect to homocysteine, have you?

A. No, I haven't.

Q. And, in fact, is your position as a manager at LabCorp a full-time occupation?

A. It keeps me busy. Yes, it is.

Q. So would you describe yourself as knowledgeable about homocysteine but not expert?

A. I'd say very knowledgeable but not expert.

Q. Okay. Now, with that said, why, to your knowledge, was there such an increase in demand for these single homocysteine tests in 1998?

A. Well, information was starting to come out that homocysteine was an independent risk factor for cardiovascular disease and thrombosis.

Q. Is cardiovascular disease and thrombosis a common condition, to your knowledge, in the American population?

A. I mean it's the No. 1 killer in the United States.

* * * *

[Page 1482, lines 5-6]

Q. You were here for Dr. McCully's testimony; right?

A. Yes, I was.

* * * *

[Page 1482, line 20 to Page 1483, line 1]

Q. Do you dispute Dr. McCully's testimony that homocysteine testing is not used to detect a patient's age, gender, alcohol intake, smoking status, renal disease, whether he has lupus, whether he has rheumatoid arthritis, whether he has hypothyroidism, or whether he has ingested drugs or toxins?

A. No, I wouldn't dispute that.

* * * *

[Page 1579, line 24 to Page 1580, line 4]

Q. Now, with respect to this range and with respect to the outcomes altogether of the several hundred thousand tests that have been done by LabCorp as a single homocysteine test, how many of them typically are raised above normal; that is, in excess of 15?

A. Less than 20 percent.

* * * *

[Page 1629, line 19 to Page 1632, line 8]

Q. Dr. Wentz, could I ask you to look at Plaintiffs' Exhibit 19.

A. Yes, I have it.

Q. Okay. Do you recognize the quote from the Ueland article: "Thus, the laboratory diagnosis of cobalamin and folate deficiency will probably account for the largest number of plasma serum homocysteine determinations"?

A. I don't recognize it, but I see it.

Q. Okay. The Ueland article is one of the references listed in the homocysteine only test description in the Directory of Services; right?

A. I'm aware of that, yes.

Q. Similarly, do you see the next quote out of the Verhoef article?

A. Yes.

Q. I won't bore everyone by reading each of these. But Verhoef also is an article listed in the references section of the Homocysteine Only Directory of Services; right?

A. That's correct.

Q. Same thing with Robinson—right—the last on the page?

A. Correct.

Q. If you'll flip over to Plaintiffs' 20.

A. I'm there.

Q. Keep going, please, to 21. These are quotes from your article; right? "Homocysteine, the bad amino acid"?

A. I'd have to cross-reference it, I guess, with the actual article.

Q. Okay. Let's not take the time to do that. And on page 2, do you see further quotes?

A. Yes.

Q. And then finally, on Plaintiffs' 22, do you see the quote from your other article, "Megaloblastic Anemia," stating, "The metabolite patterns are characteristic for the particular vitamin involved. These biochemicals pathways have been studied extensively, and the clinical implications have been described in various publications appearing over the course of more than 30 years. Subsequently, the clinical correlations and analytical methodology became the basis for two U.S. patents." And then you see the footnotes two U.S. patents, both by these three professors and the one being the one at issue in this case; right?

A. Yes. I did cite those.

Q. Now, the Directory of Services in which these references appear is used to help educate physicians about the test; right?

A. You're referring to the single homocysteine test?

Q. Yes.

A. Yeah. Those references are there because they support the information described in the test descript[ion]. They're there for that purpose.

Q. And for physicians to refer to; right?

A. Certainly they may refer to it, yes.

Q. And the articles that you wrote are used to help market the tests? Right?

A. Well, that wasn't the primary reason for writing those articles, no. It may have—I mean they make may have a marketing function.

Q. So all of this, the articles and the articl.s that you wrote, are available to LabCorp's customers, aren't they?

A. Certainly they're available through Medline, the Library of Medicine. I mean they are available, yes.

Q. In fact, they're available to the general public; right?

A. Correct.

* * * *

[Page 1689, line 5 to Page 1690, line 6]

MR. HIGGINS: Well, your Honor, on that issue, again the —because of the prosecution history, where the examiner required that second step to be added to overcome the prior art and particularly a 102 anticipation rejection, there is no equivalence on that step. And that recent Festo decision which cert. has been granted on—that decision specifically says where an element has been limited in view of a patentability rejection, then there are no equivalents.

THE COURT: Mr. Higgins, I'm probably going to agree with you on some of these, because with all due respect to Dr. Allen, who I think is a genius on what he has done, it's difficult to think you can patent an idea, rather than a test. And that's what I'm afraid some of these patents do, is try to patent an idea. And there is problems with the wording as far as—this has been, you know, shown to the jury add ad nauseum about the raised homocysteine giving rise to certain conclusions when some of the tests are not raised. However, my experience with patent cases in the 22 years or so that I've been sitting here in Federal Court is that when I try to apply common sense to some of these, invariably I get reversed. So if I deny your motions and let the jury decide them, I can always, after a verdict, reconsider; but then we have a jury verdict, so that if it is reversed, we don't have to try the case all over again. Do you know what I'm saying?

MR. HIGGINS: Oh, I understand that, your Honor. I appreciate that.

* * * *

[Page 1707, line 4 to Page 1708, line 22]

THE COURT: Let's talk about whether you really can patent an idea, though, rather than a method. If you could do this quickly. This is part of the argument. The idea that that doctor can take that high homocysteine and figure out that there is a B12 or a folate deficiency. Really what Claim 13 is.

MR. WHITEHAIR: I think there has been a misunderstanding about what this mental step might be. The mental step doctrine is pretty outdated. It turns out, in fact, that the Federal Circuit has decided that a mental step, even—as long as it in an algorithmic sequence is fully legitimate. What's really the problem with this: You remember in 1985, no one knew to make this mental step. They came out in their patent and said, Hey, look what happens if you have this high number of this special marker of the hundred thousand markers in the body. We found one that happens to be 95 percent of the time always hooked up with a B12 and folate deficiency. Wow. Now, you can go look for that marker and you can start skipping the look of all the other markers. There is this serum vitamin level, you know, B12 in your blood, folate in your blood, this homocysteine, MDS, any of that stuff. They found this one marker out of all the markers in the world. This one always responds to B12 and folate.

THE COURT: What is the invention? What is the method, not the mental step, but what is the—that's invented and why are you arguing that the Abbott test, or are you arguing that the Abbott test is covered under the patent or just under the contract?

MR. WHITEHAIR: No, unquestionably it's covered under the patent. The issue is whether Abbott is accomplishing the exact same thing that the other method was. LabCorp would like to say that they've only been paying on a royalty agree-

ment and the know-how license with Metabolite on the basis of Claims 1 through 12. That's not what the license agreement says. The license agreement very clearly divides out mass spectrometry—that's the GCMS; things covered by the claims and methods of the patent, and then there is a couple of tests that really aren't covered by the patent. And those are defined even differently as having to show some connection or correlation to B12 and folate deficiency.

* * * *

Rule 50 Motions

[Page 1727, lines 2-6]

MR. JABLONSKI: * * * I honestly think that with time and use of the jury verdict and the instructions that they can come to focus on the issues.

THE COURT: You couldn't have a brighter jury.

MR. JABLONSKI: Yes.

* * * *

Plaintiffs' Closing Argument

[Page 1769, line 24 to Page 1770, line 18]

We also see that LabCorp wrongfully terminated the Metabolite license agreement to get out of paying these royalties; and thus, the license agreement evaporates for them. That leaves us with the 21.5 percent payment for all of the assays that were done when that license agreement was wrongfully set aside and the 6 percent for all of the infringement that was done by CTI—or by LabCorp—again, when that license agreement was just shut aside.

The parties have actually gone to the trouble of coming up with a total number of Abbott assays. That's Exhibit 278. They've also totaled the actual dollar amount that has been earned on billed amounts. It comes to 16,989,000 and change. You'll see the number in the book.

CTI would ask and asks now for its 6 percent for this patent infringement or for this failure to follow the license agreement payment scheme. And 6 percent of that number comes to $1,019,364.

Metabolite: 21.5 percent on that number. And they each get their own cut at that same number because they each have an independent royalty stream. Comes to $3,652,724.

* * * *

Jury Verdict

[Page 1865, lines 8-12]

THE COURT: * * * So—and last and not least is the jury, because this is indeed one of the most complex cases that we have ever had presented in court, if not the most complex; and I think this is probably the most attentive, hard-working jury I've ever had, so I really do thank you.

* * * *

(22)

No. 04-607

DEC 2 [illegible]

IN THE

Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS (doing business as LabCorp),

Petitioner,

v.

METABOLITE LABORATORIES, INC. and COMPETITIVE TECHNOLOGIES, INC.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

JOINT APPENDIX
(Volume II of II)

JONATHAN S. FRANKLIN*
CATHERINE E. STETSON
JESSICA L. ELLSWORTH
HOGAN & HARTSON L.L.P.
555 Thirteenth Street, N.W.
Washington, D.C. 20004
(202) 637-5766

Counsel for Petitioner

GLENN K. BEATON*
GIBSON, DUNN & CRUTCHER LLP
1800 California Street
Denver, Colorado 80202
(303) 298-5773

(Additional Counsel for Respondents on Inside Cover)

Counsel for Respondents

* Counsel of Record

PETITION FOR CERTIORARI FILED NOVEMBER 3, 2004
CERTIORARI GRANTED NOVEMBER 2, 2005

Additional Counsel for Respondents:

MIGUEL A. ESTRADA
MARK A. PERRY
GIBSON, DUNN & CRUTCHER LLP
1050 Connecticut Avenue, N.W.
Washington, D.C. 20036
(202) 955-8500

MARK A. LEMLEY
KEKER & VAN NEST LLP
710 Sansome St.
San Francisco, CA 94111
(415) 391-5400

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SUPPLEMENTAL APPENDIX

United States Patent No. 4,940,658 (July 10, 1990)

The appendix to the petition for certiorari contains the following material which is omitted from the Joint Appendix:

Appendix A:

Opinion of the U.S. Court of Appeals for the Federal Circuit dated June 8, 2004 ..... 1a

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Order of the U.S. Court of Appeals for the Federal Circuit Denying Rehearing and Rehearing En Banc dated August 5, 2004 ..... 40a

Plaintiffs' Exhibit Demo. 01

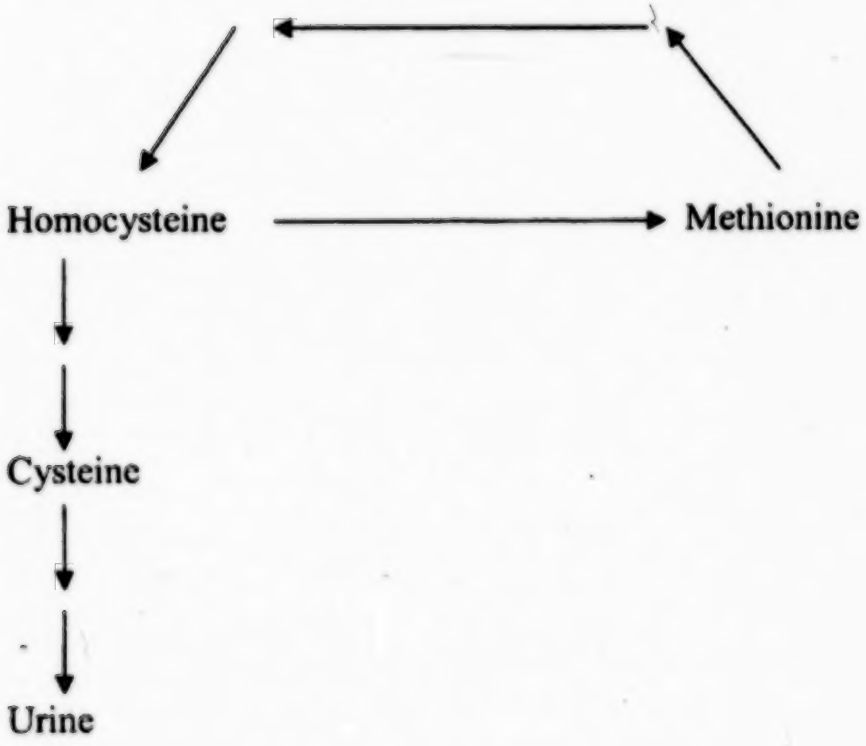
DESIRABLE TRAITS OF A USEFUL DIAGNOSTIC TEST

1. READILY FOUND – It can readily be found in blood or urine.
2. RELIABLE – It can be measured reliably.
3. STABLE – It is chemically stable over minutes or hours.
4. CONSTANT WHILE HEALTHY – The finding remains relatively constant while the patient is in healthy/normal state.
5. CORRELATES – The marker "correlates" (mutual or reciprocal relationship) with disease state compared with healthy state.
6. MEASURABLE DIFFERENCE FROM HEALTHY – There is always a measurable difference from an individual's healthy/normal range, and often a measurable difference from the population normal range.
7. TREATMENT AVAILABLE – Treatment is available that brings the test finding back toward that individual's healthy/normal range.
8. PREDICTS OUTCOME – When suggested treatment is applied, patient's healthy/normal status returns, or further deterioration is prevented.
9. EARLY WARNING SYSTEM – Marker detection indicates the diseased or impaired state in time to interrupt or reverse early physical/mental manifestations.

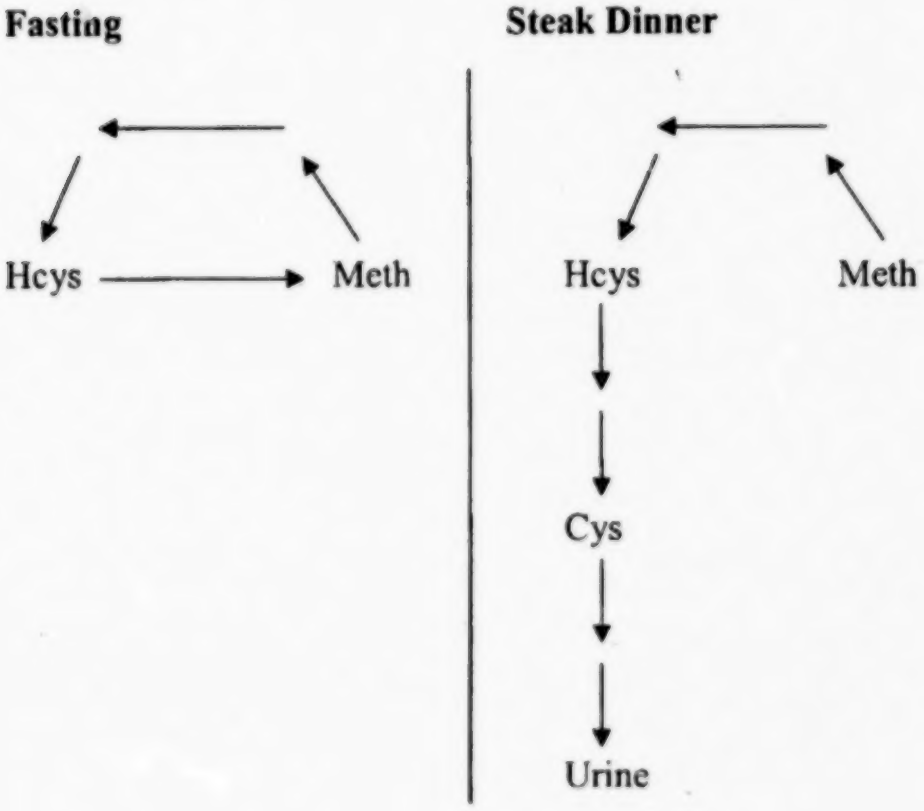
* * * *

Plaintiffs' Exhibit Demo. 02

Methionine Pathway



Plaintiffs' Exhibit Demo. 03



Plaintiffs' Exhibit Demo. 04

Key Amino Acids in Methionine Pathway

	Meth	Hcys	Cys
Building block for proteins	☑		☑
Needed for genes	☑		
Needed for > 100 different processes	☑		

Plaintiffs' Exhibit Demo. 05

Possible Metabolic Changes

	Meth	Hcys	Cys
#1 Hcys → (B_{12}+F) → Meth	—	—	—
#2 Hcys → (B_{12}+F) → Meth	↓	↑	—

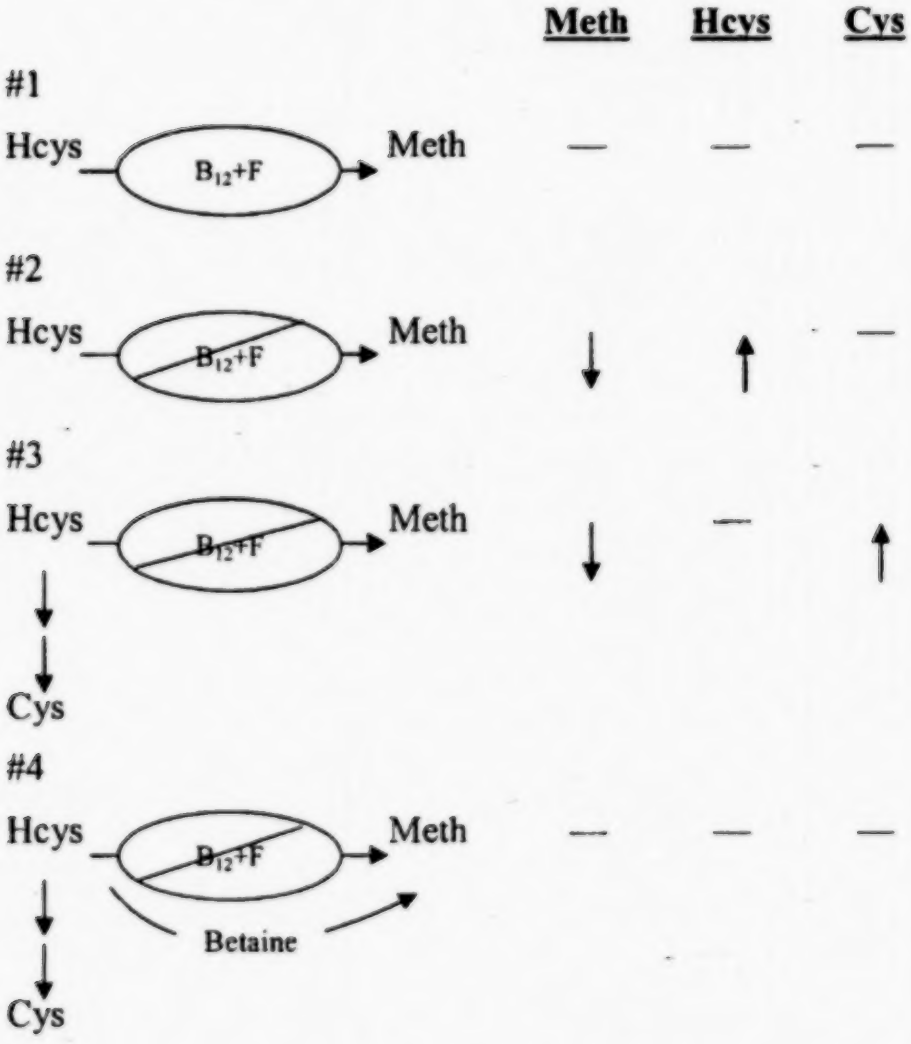
Plaintiffs' Exhibit Demo. 06

Possible Metabolic Changes

	Meth	Hcys	Cys
#1 Hcys → (B_{12}+F) → Meth	—	—	—
#2 Hcys → ~~(B_{12}+F)~~ → Meth	↓	↑	—
#3 Hcys → ~~(B_{12}+F)~~ → Meth; Hcys ↓ Cys	↓	—	↑

Plaintiffs' Exhibit Demo. 07

Possible **Metabolic Changes**



Plaintiffs' Exhibit Demo. 08

Three Basic Mechanisms that Cause Deficiencies in B_{12} and Folate

	Mechanism		
Condition	**Poor Diet**	**Poor Absorption**	**Vitamin Defect**
1. Age	☑	☑	
2. Gender	☑		
3. Smoking	☑		☑
4. Alcohol	☑	☑	☑
5. Medications		☑	☑
6. Kidney Disease	☑	☑	☑
7. Thyroid Disease		☑	☑

Plaintiffs' Exhibit Demo. 09

Use of Assays for Total Homocysteine to Detect Various Common Conditions

Condition	Used for Detection
1. Age	**NO**
2. Gender	**NO**
3. Smoking	**NO**
4. Alcohol	**NO**
5. Medications	**NO**
6. Kidney Disease	**NO**
7. Thyroid Disease	**NO**
8. B_{12} Deficiency	**YES**
9. Folate Deficiency	**YES**

Plaintiffs' Exhibit Demo. 10

Select Manifestations of B_{12} and Folate Deficiency

Manifestations	Treatment if Total Homocysteine is Elevated
Big red blood cells	**B_{12}/Folate**
Not enough red blood cells	**B_{12}/Folate**
Abnormal bone marrow	**B_{12}/Folate**
Not enough white blood cells	**B_{12}/Folate**
Sore feet and hands	**B_{12}/Folate**
Poor memory	**B_{12}/Folate**
Difficulty walking	**B_{12}/Folate**
Poor control of urination	**B_{12}/Folate**
Poor control of bowel movements	**B_{12}/Folate**
Neural tube defects	**B_{12}/Folate**
Heart attacks	**B_{12}/Folate**
Strokes	**B_{12}/Folate**

Plaintiffs' Exhibit Demo. 16

What Abbott Laboratories Teaches About Homocysteine in Its *Home Study Kit* Article *"Homocysteine: The New Risk Factor – Introduction to Patient Management"*

(© 1999)
(L000561 - L000607)

"This CME [Homestudy] activity is sponsored in part by [a Division of] Abbott Laboratories" (L000561)

"Target audience: physicians in private practices and health-care maintenance organizations, across all geographic areas, who evaluate and treat patients for coronary risk factors (eg, cardiology, internal medicine, family practice, general practice)" (L000565)

"Several vitamins function as cofactors and substrates in methionine and homocysteine metabolism, including folate, vitamin B_6, and vitamin B_{12}. A number of studies have demonstrated inverse relationships between homocysteine concentrations and levels of both folic acid and B vitamins, and these have recently been reviewed.[4]" (L000565)

"Other studies have found that vitamin supplementation can normalize homocysteine concentrations in most individuals." (L000565)

What Abbott Laboratories Teaches About Homocysteine in Its *Home Study Kit* Article *"Homocysteine: The New Risk Factor – Introduction to Patient Management"* *(cont.)*

"META-ANALYSIS OF HOMOCYSTEINE-LOWERING STUDIES. A recent meta-analysis summarized the results of 12 randomized, placebo-controlled trials in over 1,100 subjects to compare the homocysteine-lowering effects of folic acid alone or in combination with vitamin B_6 or vitamin B_{12}.[88]" (L000591)

"[T]he meta-analysis found that the use of 0.5 to 5 mg dietary folic acid daily reduced homocysteine concentrations by 25% (P <0.001). The addition of 0.5 mg vitamin B_{12} daily reduced the homocysteine levels by another 3% to 10% over the reduction with folic acid alone. However, the addition of 16.5 mg vitamin B_6 daily produced no significant supplemental reducing effect on blood homocysteine levels." (L000591)

Plaintiffs' Exhibit Demo. 18

What LabCorp's [Directory of Services] Teaches Doctors About Megaloblastic Anemia (online pp. 1-2)

Anemia Profile, Megaloblastic, Serum (706960)

"Serum methylmalonic acid and homocysteine are the primary metabolic tests for diagnosing and distinguishing between B12 and folate deficiency."

"This method is a more specific diagnostic tool for B12 and folate deficiencies as it has been shown that some patients with deficiencies will have normal or borderline serum B12 or folate."

"Elevated metabolite levels do not correct with B12, folate, or B6 treatment unless vitamin deficiency coexists."

Plaintiffs' Exhibit Demo. 19

What LabCorp's [Directory of Services] Teaches Doctors About the Homocysteine-Only Test

"Thus, the laboratory diagnosis of cobalamin and folate deficiency will probably account for the largest number of plasma/serum Hcy determinations."

Ueland, et al., *Clinical Chemistry*, 1993
Total homocysteine in Plasma or Serum: Methods and Clinical Applications (at p. 1776)

"In this population, folate was the most important determinant of plasma homocyst(e)ine, even in subjects with apparently adequate nutritional status of this vitamin."

Verhoef, et al., *American Journal of Epidemiology*, 1996
Homocysteine Metabolism and Risk of Myocardial Infarction: Relation with Vitamins B_6, B_{12} and Folate (at p. 847)

"Plasma homocysteine concentrations correlated negatively with both serum vitamin B12 and folate (Table 2). Three studies of patients with peripheral vascular disease and stroke yielded similar results (41, 50, 52)."

Robinson, et al., *Cleveland Clinic Journal of Medicine*, 1994
Homocysteine and Coronary Artery Disease (at p. 444)

What LabCorp's [Directory of Services] Teaches Doctors About the Homocysteine-Only Test

(cont.)

"The H(e) concentrations were independent of other risk factors for peripheral artherosclerotic disease, but increased H(e) was observed mainly in subjects with low concentrations of serum folate (47)."

Malinow, *Clinical Chemistry*, 1994
Plasma Homocyst(e)ine and Arterial Occlusive Diseases: A Mini-Review (at p. 175)

"The authors conclude that elevated homocyst(e)ine levels in the elderly may, in great part, be attributed to vitamin status."

Fortin and Genest, *Clinical Biochemistry, 1995*
Measurement of Homocyst(e)ine in the Prediction of Arteriosclerosis (at p. 159)

"Moderate and intermediate hyperhomocyst(e)inemia is most commonly seen in subjects with low concentrations of serum folate that are due to either inadequate nutrition or to certain medications (40, 66)."

Kang, et al., *Annual Review of Nutrition*, 1992
Hyperhomocyst(e)inemia as a Risk Factor for Occlusive Vascular Disease (at p. 282)

Plaintiffs' Exhibit Demo. 20

What LabCorp Teaches Doctors About the Treatment of Homocysteine Levels in its [Directory of Services] for the Homocysteine-Only Test

"Total homocysteine in serum/plasma is increased markedly in patients with cobalamin or folate deficiency, and decreases only when they are treated with the deficient vitamin."

Ueland, et al., *Clinical Chemistry*, 1993
Total homocysteine in Plasma or Serum: Methods and Clinical Applications (at p. 1764)

"Furthermore, our study supports the view that adequate folate intake from diet or supplements might be an important step toward normalizing homocyst(e)ine levels."

Verhoef, et al., *American Journal of Epidemiology*, 1996
Homocysteine Metabolism and Risk of Myocardial Infarction: Relation with Vitamins B_6, B_{12} and Folate (at p. 858)

"Vitamin therapy, which lowers the plasma homocysteine concentration, is simple, nontoxic, naturally occurring, and has a wide therapeutic index."

Robinson. et al., *Cleveland Clinic Journal of Medicine*, 1994
Homocysteine and Coronary Artery Disease (at p. 447)

What LabCorp Teaches Doctors About the Treatment of Homocysteine Levels in its [Directory of Services] for the Homocysteine-Only Test *(cont.)*

"The increased concentrations of H(e) are readily corrected by folic acid, occasionally supplemented with pyridoxine, vitamin B12, choline, or betaine."

Malinow. *Clinical Chemistry*, 1994
Plasma Homocyst(e)ine and Arterial Occlusive Diseases: A Mini-Review (at p. 173)

"Low-dose folic acid, vitamin B6 or both are used to reduce elevated H(e) levels in affected individuals. Resistant cases may be treated with betaine."

Fortin and Genest, *Clinical Biochemistry*, 1995
Measurement of Homocyst(e)ine in the Prediction of Arteriosclerosis (at p. 155)

"Irrespective of the etiology, moderate and intermediate hyperhomocyst(e)inemia is readily correctable by supplementation with folate and/or betaine."

Kang, et al., *Annual Review of Nutrition*, 1992
Hyperhomocyst(e)inemia as a Risk Factor for Occlusive Vascular Disease (at p. 294)

Plaintiffs' Exhibit Demo. 21

What LabCorp's [Directory of Services] Teaches Doctors About the Homocysteine-Only Test in its CME Article Entitled, *"Homocyst(e)ine-The Bad Amino Acid?"*
by Peter W. Wentz, Ph.D.
(L001307 – L001312)

"The most common cause of an elevated basal level of homocyst(e)ine is a deficiency of one of the B complex vitamins, folate in particular." (page 4)

"HOW CAN ELEVATED HOMOCYSTEINE LEVELS BE LOWERED? Vitamin therapy and dietary modification can work together to help lower plasma homocyst(e)ine levels." (page 4)

"Total homocyst(e)ine levels in normal subjects and patients with vascular disease correlate with serum levels of vitamin B12, folate and vitamin B6 and with the oral intake of these B-complex vitamins. Both oral and parenteral administration of these vitamins normalizes elevated homocyste(e)ine levels in virtually all patients with vascular disease, provided that renal insufficiency is not present." (page 4)

What LabCorp's [Directory of Services] Teaches Doctors About the Homocysteine-Only Test in its CME Article Entitled, *"Homocyst(e)ine-The Bad Amino Acid?"*

(cont.)

"The conclusion of the study indicates that all patients with folate levels below 4.4 ng/ml should have a homocyst(e)ine level measured before vitamin therapy is initiated." (page 4)

"Serum metabolite levels can be rechecked five to 15 days after vitamin therapy is initiated." (page 5)

"The most important determinants of tHcy have been identified as age and sex, folate and vitamin B12 status, and renal function. Vitamin supplementation, especially folic acid, is effective at lowering blood tHcy levels." (page 6)

Plaintiffs' Exhibit Demo. 22

What LabCorp's [Directory of Services] Teaches Doctors About The Allen/Stabler/Lindenbaum Patents in its CME Article Entitled *"Megaloblastic Anemia: Laboratory Screening and Confirmation"*

by Peter W. Wentz, Ph.D. (online)

"The metabolite patterns are characteristic for the particular vitamin involved. These biochemical pathways have been studied extensively and the clinical implications have been described in various publications appearing over the course of more than 30 years.[18-23] Subsequently, the clinical correlations and analytical methodology became the basis for two U.S. patents.[24,25]["] (page 5)

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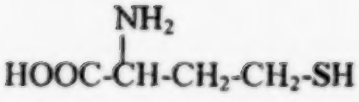
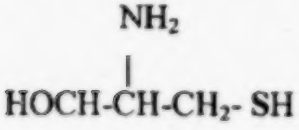
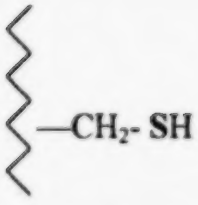
24. **United States Patent Number: 4,940,658**. Issued: July 10, 1990. Invention: Assay for sulfhydryl amino acids and methods for detecting and distinguishing cobalamin and folic acid deficiency. Inventors: Robert H. Allen, [Sally] P. Stabler, and John Lindenbaum. (at page 7 of online text)
25. **United States Patent Number: 5,374,560**. Issued: December 20, 1994. Invention: Method for screening and distinguishing between cobalamin and folic acid deficiency based on assay for cystathionine and 2-methylcitric acid. Inventors: Robert H. Allen, [Sally] P. Stabler, and John Lindenbaum. (at page 7 of online text)

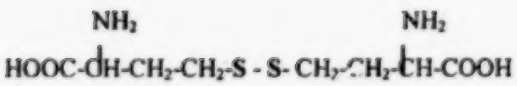
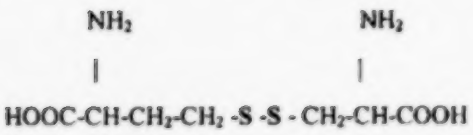
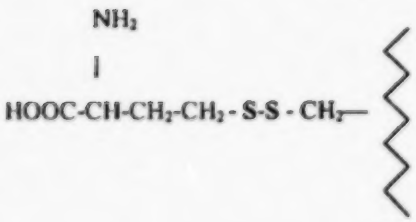
Plaintiffs' Exhibit 33

Sulfhydryl Amino Acids in Human Serum

Compound	Total Concentration (μM)	Percent of total (%)
		
HOMOCYSTEINE	8	0.6
		
CYSTEINE	400	28.4
		
ALBUMIN	1000	71.0
	1408	100.0

Plaintiffs' Exhibit 34

Forms of Homocysteine in Human Serum

Compound	Percent of total (%)	Total Concentration (μM)
		
HOMOCYSTINE	0.6	0.05
		
HOMOCYSTEINE-CYSTEINE MIXED DISULFIDE	28.4	2.27
		
HOMOCYSTEINE-ALBUMIN	71.0	5.68
	100.0	8.00

Plaintiffs' Exhibit 35

Serum Valine and Methionine Levels in Pernicious Anaemia under Treatment

J. Haemat., 1969, [16, 221]

T.E. Parry

Department of Clinical Pathology, Llaudough Hospital, United Cardiff Hospitals, Wales

SUMMARY. The serum levels of the amino acids, valine and methionine have been determined by a quantitative microbiological method in 17 cases of pernicious anaemia both before and on successive days after treatment. The results have been compared with the serum levels of the two amino acids in 16 normal subjects under similar conditions.

The serum valine level is normal in pernicious anaemia in relapse. It falls sharply during the first 48 hours following treatment, thereafter rising gradually to reach about two-thirds the pretreatment level by the fifth day. This confirms the fall in valine level in whole blood and marrow previously reported in pernicious anaemia under treatment.

The serum methionine level is subnormal in pernicious anaemia in relapse. It rises to normal in 48 hours after treatment.

Both vitamin B_{12} and folic acid are effective in lowering the serum valine and elevating the serum methionine.

The rise in serum methionine can be explained in terms of the known actions of vitamin B_{12} and folic acid. The fall in serum valine cannot at present be explained but several possibilities are discussed.

* * * *

Plaintiffs' Exhibit 41

Elevation of Total Homocysteine in the Serum of Patients with Cobalamin or Folate Deficiency Detected by Capillary Gas Chromatography-Mass Spectrometry

J. Clin. Invest., Vol. 81, Feb. 1988, [466-474]

Sally P. Stabler,* Paul D. Marcell,* Elaine R. Podell,* Robert H. Allen,* David G. Savage,** and John Lindenbaum**

**Divisions of Hematology and Oncology, Department of Medicine, and the Department of Biochemistry, Biophysics, and Genetics, University of Colorado Health Sciences Center, Denver, Colorado 80262; **and Department of Medicine, Harlem Hospital Center, Columbia-Presbyterian Medical Center and College of Physicians & Surgeons, Columbia University, New York, New York 10032*

Abstract

To determine if levels of serum total homocysteine are elevated in patients with either cobalamin or folate deficiency, we utilized a new capillary gas chromatographic-mass spectrometric technique to measure total homocysteine in the serum of 78 patients with clinically confirmed cobalamin deficiency and 19 patients with clinically confirmed folate deficiency. Values ranged from 11 to 476 μmol/liter in the cobalamin-deficient patients and 77 of the 78 patients had values above the normal range of 7-22 μmol/liter as determined for 50 normal blood donors. In the cobalamin-deficient patients, serum total homocysteine was positively correlated with serum folate, mean corpuscular volume, serum lactate dehydrogenase, serum methylmalonic acid, and the degree of neurologic involvement, and inversely correlated with platelets and hematocrit. In the folate-deficient

patients, values for serum total homocysteine ranged from 17 to 185 μmol/liter and 18 of the 19 patients had values above the normal range. Some patients with pernicious anemia who were intermittently treated with cyanocobalamin were found to have elevated serum levels of total homocysteine while they were free of hematologic and neurologic abnormalities. The measurement of serum total homocysteine will help define the incidence of cobalamin deficiency and folate deficiency in various patient populations.

* * * *

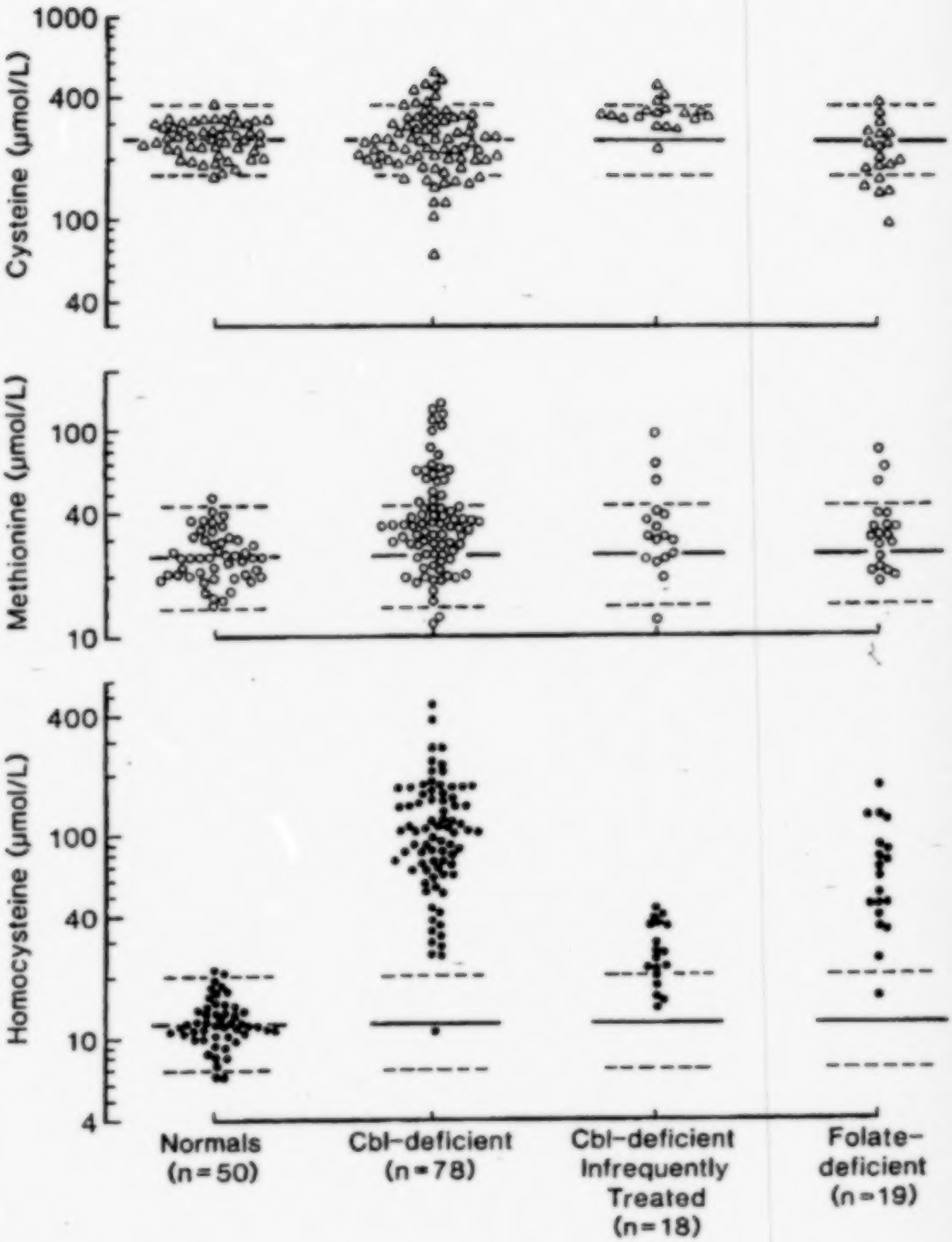

Cysteine (µmol/L)
1000
400
100
40
Methionine (µmol/L)
100
40
10
Homocysteine (µmol/L)
400
100
40
10
4
Normals (n=50)
Cbl-deficient (n=78)
Cbl-deficient Infrequently Treated (n=18)
Folate-deficient (n=19)

Figure 2. Levels of serum total homocysteine (*bottom*), serum methionine (*middle*), and serum total cysteine (*top*) in patients with clinically confirmed Cbl deficiency, folate deficiency, and Cbl-deficient infrequently treated patients who had no hematologic or neurologic abnormalities, using capillary gas chromatography-mass spectrometry. The normal range for total homocysteine is (7-22 μmol/liter), for methionine (14-44 μmol/liter), and for cysteine (173-378 μmol/liter). These ranges were calculated as the mean ± 2 SD after log transformation to correct for skewness towards higher values.

* * * *

Plaintiffs' Exhibit 66

Cost-effectiveness of Vitamin Therapy to Lower Plasma Homocysteine Levels for the Prevention of Coronary Heart Disease[:] Effect of Grain Fortification and Beyond

JAMA, August 22/29, 2001—Vol. 286, No. 8, [936-943]

Jeffrey A. Tice, MD; Elizabeth Ross, MD; Pamela G. Coxson, PhD; Irwin Rosenberg, MD; Milton C. Weinstein, PhD; M.G. Myriam Hunink, MD, PhD; Paula A. Goldman, MPH; Lawrence Williams, MS; Lee Goldman, MD, MPH

Context A high homocysteine level has been identified as an independent modifiable risk factor for coronary heart disease (CHD) events and death. Since January 1998, the US Food and Drug Administration has required that all enriched grain products contain 140 μg of folic acid per 100 g, a level considered to decrease homocysteine levels.

Objectives To examine the potential effect of grain fortification with folic acid on CHD events and to estimate the cost-effectiveness of additional vitamin supplementation (folic acid and cyanocobalamin) for CHD prevention.

Design and Setting Cost-effectiveness analysis using the Coronary Heart Disease Policy Model, a validated, state-transition model of CHD events in adults aged 35 through 84 years. Data from the third National Health and Nutrition Examination Survey (NHANES III) were used to estimate age- and sex-specific differences in homocysteine levels.

Intervention Hypothetical comparison between a diet that includes enriched grain products projected to increase folic acid intake by 100 μg/d with the same diet without folic acid fortification; and a comparison between vitamin therapy that consists of 1 mg of folic acid and 0.5 mg of cyanocobalamin and the diet that includes grains fortified with folic acid.

Main Outcome Measures Incidence of myocardial infarction and death from CHD, quality-adjusted life-years (QALYs) saved, and medical costs.

Results Grain fortification with folic acid was predicted to decrease CHD events by 8% in women and 13% in men, with comparable reductions in CHD mortality. The model projected that, compared with grain fortification alone, treating all patients with known CHD with folic acid and cyanocobalamin over a 10-year period would result in 310000 fewer deaths and lower costs. Over the same 10-year period, providing vitamin supplementation in addition to grain fortification to all men aged 45 years or older without known CHD was projected to save more than 300000 QALYs, to save more than US $2 billion, and to be the preferred strategy. For women without CHD, the preferred vitamin supplementation strategy would be to treat all women older than 55 years, a strategy projected to save more than 140000 QALYs over 10 years.

Conclusions Folic acid and cyanocobalamin supplementation may be cost-effective among many population subgroups and could have a major epidemiologic benefit for primary and secondary prevention of CHD if ongoing clinical trials confirm that homocysteine-lowering therapy decreases CHD event rates.

* * * *

Plaintiffs' Exhibit 87

Harrison (1987)
Principles of Internal Medicine

"The finding of significant macrocytosis . . . suggests the presence of megaloblastic anemia. If the macrocytosis is marked (MCV >110 fl), the patient is much more likely to have a megaloblastic anemia."

"It should be emphasized that occasionally neurologic disease may occur in a patient with a normal hematocrit."

"The normal range of vitamin B_{12} in serum is 200 to 900 pg/ml; values less than 100 pg/ml indicate clinically significant deficiency."

Plaintiffs' Exhibit 89

Rakel (1984)
Practice of Family Medicine

"The diagnosis of pernicious anemia should be suspected in an elderly individual who develops macrocytic, megaloblastic anemia while consuming a normal diet."

"Oval macrocytes are the characteristic abnormality in the blood and their presence results in a greatly increased value for the MCV."

"The anemia varies in degree but the blood hemoglobin level is less than 7 or 8 gm/dl in symptomatic patients."

"In vitamin B_{12} deficiency, serum vitamin B_{12} is greatly reduced (less than 100 pg/ml) whereas the serum folate is normal."

Plaintiffs' Exhibit 91

Jandl (1987)
Blood: Textbook of Hematology

". . . [the MCV is] usually over 115 fl but commonly 130-150 fl . . ."

". . . the white count . . . ordinarily is between 3,000 and 4,000 cells/ul . . ."

"Platelet counts are subnormal in nearly all patients . . ."

"LDH levels average about 15 times normal in megaloblastic anemia . . ."

"Concentrations [of serum B_{12}] below 100 pg/ml indicate vitamin B_{12} deficiency sufficient to cause megaloblastic anemia."

Plaintiffs' Exhibit 93

Cecil (1985)
Textbook of Medicine

"Neurologic .symptoms occur later in some but not all patients. Curiously, they can occur in the absence of megaloblastic anemia."

"A decreased serum vitamin B_{12} level is decisive diagnostic evidence. Clinical signs generally appear when the serum level is below 80 to 100 pg per milliliter."

"Methylmalonic aciduria is also a sensitive index of vitamin B_{12} deficiency."

"In practice, assay of urinary methylmalonate is rarely necessary."

Plaintiffs' Exhibit 95

Are Hematology and Medical Textbooks Correct in What They Tell us About the Clinical Spectrum of Cbl Deficiency?

Approach

1. Develop new methods for measuring metabolic parameters in Cbl deficient patients.

AND

2. Perform careful clinical studies with Cbl deficient patients.

Plaintiffs' Exhibit 108

NEUROPSYCHIATRIC DISORDERS CAUSED BY COBALAMIN DEFICIENCY IN THE ABSENCE OF ANEMIA OR MACROCYTOSIS

New England Journal of Medicine 318:1720-1728 (June 30), 1988

* * * *

John Lindenbaum, M.D., Edward B. Healton, M.D., David G. Savage, M.D., John C.M. Brust, M.D., Thomas J. Garrett, M.D., Elaine R. Podell, B.A., Paul D. Marcell, B.S., Sally P. Stabler, M.D., and Robert H. Allen, M.D.

Abstract Among 141 consecutive patients with neuropsychiatric abnormalities due to cobalamin deficiency, we found that 40 (28 percent) had no anemia or macrocytosis. The hematocrit was normal in 34, the mean cell volume was normal in 25, and both tests were normal in 19. Characteristic features in such patients included paresthesia, sensory loss, ataxia, dementia, and psychiatric disorders; longstanding neurologic symptoms without anemia; normal white-cell and platelet counts and serum bilirubin and lactate dehydrogenase levels; and markedly elevated serum concentrations of methylmalonic acid and total homocysteine. Serum cobalamin levels were above 150 pmol per liter (200 pg per millileter) in 2 patients, between 75 and 150 pmol per liter (100 and 200 pg per milliliter) in 16, and below 75 pmol per liter (100 pg per milliliter) in only 22.

Except for one p[illegible]ho died during the first week of treatment, every patient in this group benefited from cobalamin therapy. Responses included improvement in neuropsychiatric abnormalities (39 of 39), improvement (often within

the normal range) in one or more hematologic findings (36 of 39), and a decrease of more than 50 percent in levels of serum methylmalonic acid, total homocysteine, or both (31 of 31).

We conclude that neuropsychiatric disorders due to cobalamin deficiency occur commonly in the absence of anemia or an elevated mean cell volume and that measurements of serum methylmalonic acid and total homocysteine both before and after treatment are useful in the diagnosis of these patients.

* * * *

Table 3. Neuropsychiatric Abnormalities and Responses to Treatment in 40 Patients.

Abnormality	No. of Patients	Response to Cobalamin Therapy			
		Complete	Partial	None	Unknown
Impaired vibration sense	31	9	13	2	7
Paresthesia	30	21	9	-	-
Impaired position sense	22	11	7	-	-
Impaired touch or pain perception	17	9	6	1	1
Ataxia	17	12	4	-	1
Abnormal gait	15	7	5	-	3
Memory loss	13	8	3	-	2
Decreased reflexes	9	4	2	-	3
Weakness	9	8	1	-	-
Decreased muscle strength	7	5	2	-	-
Psychiatric disorders	7	5	-	1	1
Romberg's sign	7	3	3	-	1
Fatigue	6	6	-	-	-
Urinary or fecal incontinence	4	3	1	-	-
Increased reflexes	3	1	1	-	1
Babinski's signs	3	-	-	3	-
Lhermitte's sign	3	3	-	-	-
Disorientation	3	1	1	-	1
Spasticity	2	-	1	1	-
Obtundation	1	-	-	-	1
Urinary urgency or nocturia	1	1	-	-	-
Impotence	1	1	-	-	-
Decreased vision or optic atrophy	1	1	-	-	-

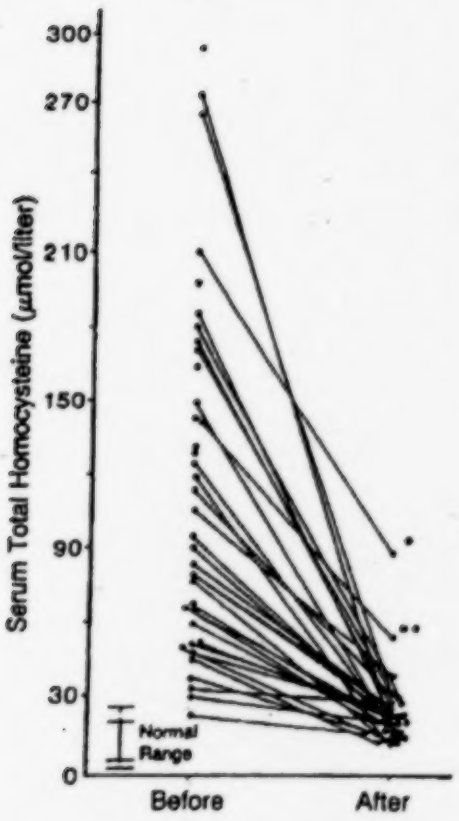


Figure 2. Serum Total Homocysteine Concentrations before and after Therapy with Cyanocobalamin.

The bars connected by unbroken lines indicates the normal range, on the basis of the mean ±2 SD (7 to 22 μmol per liter); the bars connected by broken lines indicate 3 SD above and below the mean (6 to 29 μmol per liter). One asterisk indicates serum obtained one day after a single injection of cyanocobalamin; two asterisks, serum obtained five days after a single injection.

* * * *

Plaintiffs' Exhibit 109

EDITORIAL

COBALAMIN AND THE NERVOUS SYSTEM

New England Journal of Medicine 318:1752-1754 (June 30), 1988

* * * *

The second report[6] considers problems that are anything but rare. In a large series of patients with "neuropsychiatric abnormalities," the authors conclude that such commonplace manifestations as paresthesias, ataxias, memory loss, weakness, personality and mood changes, and fatigue were due to cobalamin deficiency. The disorder was diagnosed according to laboratory tests, including assays for serum methylmalonic acid and homocysteine, the sensitivity of which, the authors suggest, made them notably helpful, since anemia was not present, the results of the Schilling test were normal, and serum cobalamin levels were not depressed. It is interesting and perhaps noteworthy that many of the patients were free of these traditional signs of cobalamin deficiency. If confirmed, this finding is important for obvious reasons. For one, it should influence the way we care for our patients. For another, it extends the perimeter of cobalamin-deficiency neuropathy to include much of what may be termed the neuropsychopathology of everyday life.

Here, perhaps, is the possible basis for a reservation or two. Symptoms such as those mentioned above are notoriously difficult to deal with quantitatively or to control in clinical experiments. They may have many causes, and as the authors acknowledge, they wax and wane. It also gives one pause to note that many of the patients supposed to have cobalamin deficiency had no recognizable cause of the

deficiency—and one need not be an obdurate skeptic to notice the authors' reliance on new diagnostic tests that gave abnormal results (many in patients with no known disease) when the results of more traditional tests were normal. The importance of such results will be weighed more easily as we gain experience with these procedures, which raise anew an old problem: How do we best diagnose a deficiency of a nutrient? It would appear that measurement of serum levels of the nutrient may not always be the answer, as many of us have suspected.

Finally, we are urged to look for cobalamin deficiency in patients with "unexplained" neuropsychiatric disorders (have any neuropsychiatric disorders been explained?), and if that is not possible, to administer cobalamin therapy anyway. This, of course, would add new costs to medical care, but if real benefits await these patients, the costs are justified. At the least, one can hope that physicians will try to gather meaningful data before giving everyone cobalamin in an uncritical manner, and that they will observe the results of cobalamin therapy in their patients. Although these findings are provocative and encouraging, we do need confirmatory data. Could it be that the many cobalamin injections over the years for vague symptoms were in fact justified?

Massachusetts General Hospital
Boston, MA 02114 WILLIAM S. BECK, M.D.

* * * *

REFERENCES

* * * *

6. Lindenbaum J, Healton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med 1988; 318:1720-8.

Plaintiffs' Exhibit 112

Prospective Evaluation of the Clinical Spectrum of Cbl Deficiency

1. From 9/83 to 8/85 there were 7747 serum samples submitted for assay of Cbl at Harlem Hospital and Columbia Presbyterian Hospital in New York.

2. The serum Cbl was <200 pg/ml in 300 samples.

3. In the low Cbl group, 86 patients were judged to be Cbl deficient based on one or more objective responses to Cbl therapy.

Plaintiffs' Exhibit 113

Responses to Cbl Therapy in 86 Consecutive Patients with Clinically Confirmed Cbl Deficiency

Response	Percent
Increase in hematocrit >0.05	50
Decrease in MCV >5 fl	81
Correction of peripheral smear	48
Clear neuropsychiatric improvement	28
1 response	33
2 responses	31
3 responses	33
4 responses	3

(24/26 patients with neuropsychiatric responses also had one or more hematologic responses)

(85/86 patients had elevations of methylmalonic acid and homocysteine that corrected with Cbl therapy)

Plaintiffs' Exhibit 114

Pretreatment Laboratory Tests in 86 Consecutive Patients with Clinically Confirmed Cbl Deficiency

Test Result	Percent
Not Anemic	44
Not Macrocytic	36
Normal WBC	84
Normal Platelets	79
Normal Peripheral Smear	32
Normal LDH	43
Normal Bilirubin	83
Normal Gastrin	37
Absent IF Antibodies	51
Normal Schilling Test	14
Serum Cbl >100 pg/ml	38

Plaintiffs' Exhibit 122

Conclusions Concerning the Clinical Spectrum and Diagnosis of Cbl Deficiency

1. Much more varied than previously believed.
2. Neuropsychiatric abnormalities occur frequently in the absence of the classic hematologic abnormalities.
3. Serum Cbl levels are often >100 pg/ml and may be normal, even in patients with severe Cbl deficiency.
4. Serum methylmalonic acid and homocysteine levels are useful supplements to the serum Cbl assay.
5. Don't believe everything you read in medicine and subspecialty textbooks.
6. Even old fashioned diseases need to be restudied from time to time.

Plaintiffs' Exhibit 125

Neuropsychiatric Consequences of Cobalamin Deficiency

Advances in Internal Medicine (Stollerman, ed.) Vol. 36, [33-56]

1991

William S. Beck, M.D.

Professor of Medicine, Department of Medicine, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts

Editor's Introduction

The history of vitamin B_{12} is a 20th-century classic in clinical investigation: inquiry at the bedside, self-experimentation, integration of vexing observations on domestic and laboratory animals and microbiologic species, all culminating in sophisticated chemical identification and synthesis of the cobalamin molecule. Pernicious anemia and other well-known forms of vitamin B_{12} deficiency were promptly and unequivocally responsive to the pure vitamin.

Included were some of the neuropsychiatric changes provided they were of reasonably short duration. The more chronic neuropsychiatric syndromes did not show dramatic responses. Claims to the contrary were based on anecdotal reports and uncontrolled studies that such commonplace complaints as memory loss, weakness, fatigue, and personality and mood changes were benefited.

The question has been reopened, however, by new studies, which appear valid, in which improvement has been described in neuropsychiatric syndromes by the use of vitamin B_{12} even in patients in whom there is no anemia and in whom some of the conventional assays for vitamin B_{12}

deficiency have yielded either equivocal or normal results. Now, with improved methods and new insights into possible advantages of different forms of cobalamin, there is renewed ferment after 30 years of, it appears, unwarranted complacency.

For the past 35 years, Dr. Beck has been in the forefront of studies on Vitamin B_{12}, its chemistry and physiology, and is without equal as an objective authority in providing a critical and valuable appraisal of what may be expected from these provocative recent studies.

Gene H. Stollerman, M.D.

* * * *

[Excerpt from Dr. Beck's chapter:]

Serum Methylmalonic Acid and Homocysteine.

* * * *

More recent work[80] indicates that 95% of patients who relapse because of suboptimal therapy display early elevations of serum methylmalonic acid, total homocysteine, or both metabolites, compared with 69% with low serum cobalamin levels. Of 419 consecutive patients with recognized significant cobalamin deficiency, 12 had serum cobalamin levels greater than 200 pg/mL, mild or absent anemia, and (in 5) prominent neurologic signs that responded to cobalamin. In all 12 cases, both serum methylmalonic acid and total homocysteine values were increased. Observations by others[81] confirm the value of total homocysteine assays in cobalamin deficiency. Such data, it would appear, establish that serum cobalamin is normal in a significant minority of cobalamin-deficient patients and that assay of these serum metabolites is diagnostically essential.

* * * *

Commentary

For years, we have seen inconclusive reports suggesting that neurologic symptoms attributable to cobalamin deficiency are more varied and complex than those of subacute combined system disease. Needless to say, the failure of early observers to prove a causal connection between cobalamin deficiency and certain neurologic symptoms did not prove there is no connection.

Such proof may be at hand. The new work summarized above strongly supports the claim that determinations of serum methylmalonic acid and total homocysteine provide a new diagnostic standard against which other procedures are henceforth to be compared and evaluated. The use of these tests has provided compelling evidence that intracellular cobalamin deficiency can and often does exist in the absence of megaloblastic anemia or low serum cobalamin levels.

* * * *

Plaintiffs' Exhibit 126

37 Consecutive Alcoholic Patients with Anemia and Megaloblastic Bone Marrows

Folate	< 2.1 ng/ml	15/37 (41%)
Homocysteine	> 22 μM	34/37 (92%)
	> 30 μM	27/37 (73%)

Plaintiffs' Exhibit 132

CONFIDENTIAL

LICENSE AGREEMENT

THIS AGREEMENT, made effective as of this 22nd day of November 1988, by and between UNIVERSITY PATENTS, INC., a corporation of the State of Delaware (hereinafter referred to as "UPI"), and METABOLITE LABORATORIES, INC., a Colorado corporation, having a place of business at No. 4001 S. Dexter Street, Inglewood, Colorado 80110 (hereinafter referred to as "LICENSEE");

WITNESSETH:

WHEREAS, ROBERT H. ALLEN and SALLY P. STABLER, members of the faculty and staff of the UNIVERSITY OF COLORADO, and JOHN LINDENBAUM, a member of the faculty and staff of COLUMBIA UNIVERSITY, are co-inventors of United States Patent Application Serial No. 933,553, filed on November 20, 1986 and entitled: "Assay For Sulfhydryl Amino Acids and Methods for Detecting and Distinguishing Cobalamin and Folic Acid Deficiency", a copy of which is appended hereto and marked "Attachment 1"; and

WHEREAS, the portion of the Invention developed by ROBERT H. ALLEN and SALLY P. STABLER is the property of UNIVERSITY OF COLORADO FOUNDATION, INC., and the portion of the Invention developed by JOHN LINDENBAUM is the property of THE TRUSTEES of COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK: and

WHEREAS, UPI has the exclusive right to license to others the aforementioned United States Patent Application, together with any patents which may issue thereon throughout the world, as evidenced by a certain Service Agreement by and between UNIVERSITY OF COLORADO FOUNDATION, and THE TRUSTEES OF COLUMBIA UNI-

VERSITY IN THE CITY OF NEW YORK and UPI, a copy of which is appended hereto and marked "Attachment 2"; and

WHEREAS, LICENSEE intends to conduct the business of a reference laboratory whereunder it will perform diagnostic assays for physicians and for commercial diagnostic laboratories, reporting to said physicians and laboratories results of said assays for use by said physicians and transmittal by said laboratories to its customers; and

WHEREAS, LICENSEE desires to obtain a nonexclusive license from UPI under such patent application and patents;

NOW THEREFORE, in consideration of these premises and of the mutual covenants hereinafter set forth, UPI and LICENSEE mutually covenant and agree as follows:

ARTICLE I - DEFINITIONS

For the purpose of this Agreement, the following terms shall have the indicated meanings:

1.01 The term "Invention" shall mean any and all inventions made by ROBERT H. ALLEN and SALLY P. STABLER at the UNIVERSITY OF COLORADO and JOHN LINDENBAUM at COLUMBIA UNIVERSITY disclosed in a certain United States patent application entitled: "Assay for Sulfhydryl Amino Acids and Methods for Detecting and Distinguishing Cobalamin and Folic Acid Deficiency".

1.02 The term "Licensed Patents" shall mean United States Patent Application 933,553 filed on November 20, 1986 and entitled: "Assay for Sulfhydryl Amino Acids and Methods for Detecting and Distinguishing Cobalamin and Folic Acid Deficiency", including any patents issuing therefrom, and continuations, continuations-in-part, divisions and/or reissues thereof and to which UPI has or shall have the right to grant licenses during the term hereof.

1.03 The term "Licensed Process(es)" shall mean any assays conducted in accordance with the Invention.

1.04 The, term "Sales" shall mean the amount charged by a physician or commercial diagnostic laboratory to his patient or its customer for providing to said patient or customer the results of any assay performed by LICENSEE in accordance with the Invention, without any deduction therefrom.

1.05 "Confidential Information" shall mean all information, expertise, and technology relating to the formulation, development and commercialization of Licensed Process which is communicated to LICENSEE hereunder (including communications by or from ROBERT H. ALLEN to LICENSEE pursuant to any agreement between them or between LICENSEE and the UNIVERSITY OF COLORADO), except for such part thereof that was, at the time of the disclosure, already known to LICENSEE, patented, previously disclosed in a publication, or otherwise in the public domain, or such part thereof that subsequently becomes patented, disclosed to LICENSEE or in a publication by a third party having a right to make such disclosure or otherwise becomes within the public domain through no fault of the receiving party.

1.06 The term "License Year" shall mean a twelve month period of time commencing on the first day of January, April, July or October next following the date of this Agreement, and each twelve (12) month period thereafter.

ARTICLE II - GRANT BY UPI

2.01 Subject to the terms and conditions of this Agreement and to the provisions of 35 USC 200-212 as implemented by 37 CFR part 401, a copy of which is appended hereto as "Attachment 3", UPI agrees to grant and hereby grants to LICENSEE a nonexclusive license under the Licensed Patents, which license shall be for the practice of Licensed Process in the United States.

2.02 The license hereby granted by UPI shall not include the right of LICENSEE to grant any sublicenses.

2.03 If UPI shall hereafter grant, at any time during the term of this Agreement, a license which grants rights

granted hereunder to LICENSEE under the Licensed Patents at a more favorable royalty rate or any other more favorable terms than those provided for in this Agreement, LICENSEE shall be entitled to receive the same more favorable royalty rate or any other more favorable terms specified with respect to such Licensed Patents, subject to the other less favorable terms and conditions under which such more favorable royalty rate or other terms have been granted, provided that any such modification of this Agreement, which shall be by written amendment, shall be effective only for the period such more favorable royalty rate or other more favorable terms are in effect under such license. The foregoing shall not apply:

(1) where UPI receives monetary consideration for such license; or

(2) where LICENSEE elects to continue paying royalties on the basis set forth in this Agreement.

ARTICLE III - REMITTANCES UNDER THE LICENSE

3.01 In consideration of the grant made in ARTICLE II, LICENSEE agrees to pay UPI in respect to Licensed Processes conducted by or for LICENSEE a royalty in an amount equal to six percent (6%) of the cumulative Sales of LICENSEE'S customers, excepting therefrom such customers who are licensees of UPI under the Licensed Patents and who have direct royalty obligations to UPI thereunder.

Plaintiffs' Exhibit 143

University of Colorado Health Sciences Center
Department of Medicine
Division of Hematology

Campus Box B170
4200 East Ninth Avenue
Denver, Colorado 80262
(303) 270-8474

School of Medicine

June 4, 1992

Dr. Peter W. Wentz
Director of Toxicology
Roche Biomedical Laboratories
1447 York Court
Burlington, NC 27296

Dear Peter,

As we discussed on the telephone yesterday, I am very pleased that things are running smoothly with you in terms of the performance of the metabolite assays. I will always be glad to answer any technical questions that arise concerning the metabolite assays and Dr. Sally P. Stabler and myself will be glad to answer any questions that physicians might have regarding the results or interpretations of the metabolite assays.

One aspect of the metabolite assays that I did not mention in our conversations concerns the occasional request that only one of the metabolites be performed rather than all four. I have always refused to do this because I do not believe that it is good medical practice. My reasoning is based on the fact that a normal value for one metabolite does not exclude the possibility that one or more of the additional metabolites may be elevated as well as the fact that an isolated elevated

value for one metabolite can not be interpreted completely without knowing whether the other metabolites are also elevated or are normal. There are also technical and possible economic reasons for not separating the metabolite assays but these are overshadowed by the importance of good medical practice as just noted above. If you have any questions about this aspect of the metabolites or if this becomes an issue in the future, I hope you will feel free to ask me for any assistance that I might provide in this matter.

I am also enclosing four tables that might serve as a starting point for a brochure or physician education piece about the indications, utility and interpretation of the metabolite assays. You may want to alter the normal ranges that I have listed for serum vitamin B_{12} and folate to match those of Roche Biomedical Laboratories and I hope that you and your marketing people will feel free to make any other changes that you believe would be helpful. I am also enclosing reprints of several articles that you may wish to list as a bibliography at the end of an education piece regarding the metabolite assays.

Please let me know if I can be of any further assistance.

With best regards,

Sincerely yours,

/s/

Robert H. Allen, M.D.
Professor of Medicine
Professor of Biochemistry
Director, Division of Hematology

RHA:vla
Enclosures

Plaintiffs' Exhibit 144

FAX COVER SHEET

University of Colorado Health Sciences Center

DATE: August 25, 1992

TO: Dr. Peter W. Wentz, Director of Toxicology

LOCATION: Roche Biomedical Laboratories

PHONE NUMBER: 1-800-334-5161

FAX NUMBER: 1-919-584-0865

FROM: Dr. Robert H. Allen

FAX: (303) 270-8477

NUMBER OF PAGES INCLUDING COVER SHEET: 7

MESSAGE: Dr. Allen would like for you to call him once you have had a chance to review the attached articles. Thank You!

Sent by: Valarie Allen
Secretary
Hematology Division

IF YOU DO NOT RECEIVE ALL OF THE PAGES, PLEASE CALL THE DIVISION OF HEMATOLOGY AS SOON AS POSSIBLE AT (303) 270-8474. THANK YOU.

The Wall Street Journal
Wednesday, August 19, 1992

TECHNOLOGY & HEALTH

Certain Amino Acid Increases the Risk Of Heart Attacks

* * * *

New Data Say Most Vulnerable Are People With Poor Diets And Genetic Predisposition

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By David Stepp

Staff Reporter of the Wall Street Journal

BOSTON – A study here showed that high levels of a rarely measured blood constituent are associated with a tripling of heart-attack risk.

The finding suggests that the substance, homocysteine, poses substantial risk of heart disease in people with poor diets or with a genetic predisposition to high levels of the chemical.

But the risk can be offset by dietary supplements of vitamin B-6 or a related vitamin called folic acid, which help metabolize homocysteine, said Mier Stampfer, a researcher at Brigham and Women's Hospital here and co-author of the report. The report appears in today's issue of the Journal of the American Medical Association.

Heart Disease at Early Age

Homocysteine, an amino acid, is normally formed in the body as proteins are broken down. In previous studies, scientists found that its levels are elevated in people with an inherited disease, called homocysteinuria, which causes heart disease at an early age, said Dr. Stampfer. High levels of

homocysteine also have been previously linked to increased risk of stroke. Scientists believe that the substance is toxic to cells lining the walls of blood vessels.

In the latest study, researchers analyzed blood samples from 14,916 male physicians that were collected as part of a larger research project called the Physicians Health Study. In a five-year follow-up, 271 of the doctors had heart attacks. A comparison of homocysteine levels in the men who suffered heart attacks, with levels in those who didn't, showed that men with markedly elevated amounts of the substance were 3.4 times more likely to have attacks.

Only about 5% of the men were in the high-risk category. Their high levels of homocysteine probably represented "a mixed bag" of metabolic problems and dietary deficiencies, rather than cases of homocysteinuria, said Dr. Stampfer.

'Well-Fed Doctors'

"These were well-fed doctors," he added. "In the general population, maybe 10% have higher-than-optimal levels of homocysteine," due to a greater proportion of vitamin deficiency than experienced among the doctors. Vitamin B-6, the corrective for high homocysteine levels, is found in cereal grains, vegetables, milk, yeast and other foods.

Dr. Stampfer said that high levels of homocysteine may account for at least some of the cases of early heart attacks that aren't associated with major risk factors, such as smoking or high cholesterol levels. He added that unlike the pattern of risk for other contributors to heart disease, the risk associated with homocysteine doesn't appear to rise gradually as levels of the substance go up. Instead, the elevated risk was present in men with abnormal homocysteine levels above a certain threshold.

More research is needed to establish whether heart-attack risks in people with high homocysteine can be lowered by vitamin supplements, Dr. Stampfer cautioned. However,

even if that is proven, making practical use of the finding may be difficult; currently, few hospitals or medical laboratories are equipped to measure homocysteine levels.

* * * *

A Prospective Study of Plasma Homocyst(e)ine and Risk of Myocardial Infarction in US Physicians

JAMA, August 19, 1992— Vol 268, No. 7 at 877-881

Meir J. Stampfer, MD; M. Rene Malinow, MD; Walter C. Willett, MD; Laura M. Newcomer; Barbara Upson; Daniel Ullmann, MPH; Peter V. Tishler, MD, Charles H. Hennkens, MD

Objective.-To assess prospectively the risk of coronary heart disease associated with elevated plasma levels of homocyst(e)ine.

Design.-Nested case-control study using prospectively collected blood samples.

Setting.-Participants in the Physicians' Health Study.

Participants.-A total of 14916 male physicians, aged 40 to 84 years, with no prior myocardial infarction (MI) or stroke provided plasma samples at baseline and were followed up for 5 years. Samples from 271 men who subsequently developed MI were analyzed for homocyst(e)ine levels together with paired controls, matched by age and smoking.

Main Outcome Measure.-Acute MI or death due to coronary disease.

Results.-Levels of homocyst(e)ine were higher in cases than in controls (11.1±4.0 [SD] vs 10.5±2.8 nmol/mL; P=.03). The difference was attributable to an excess of high values among men who later had MIs. The relative risk for the highest 5% vs the bottom 90% of homocyst(e)ine levels was 3.1 (95% confidence interval, 1.4 to 6.9; P=.005). After

additional adjustment for diabetes, hypertension, aspirin assignment, Quetelet's Index, and total/high-density lipoprotein cholesterol, this relative risk was 3.4 (95% confidence interval, 1.3 to 8.8) (P=.01). Thirteen controls and 31 cases (11%) had values above the 95th percentile of the controls.

Conclusions.-Moderately high levels of plasma homocyst(e)ine are associated with subsequent risk of MI independent of other coronary risk factors. Because high levels can often be easily treated with vitamin supplements, homocyst(e)ine may be an independent, modifiable risk factor.

* * * *

Elevated homocyst(e)ine levels can often be normalized by modest doses of folate (1 to 5 mg/d).[30,34] For cases that are resistant to this therapy, the addition of vitamin B_6, choline, or betaine is often effective.[35,36] These supplements have few or no side effects under most circumstances.

* * * *

Plaintiffs' Exhibit 145

Roche Biomedical Laboratories
a subsidiary of Hoffman-LaRoche Inc.

October 30, 1992

Roche Biomedical Laboratories, Inc.
P.O. Box 2230
Burlington, North Carolina 27216-2230

Robert H. Allen, M.D.
UC Health Sciences Center
Campus Box B170
4200 East Ninth Avenue
Denver, Colorado 80262

Telephone: 919-584-5171
Cable: Biomed

RE: Serum Homocysteine Ordered as a Single Test Comment to Accompany Report

Dear Bob,

As we discussed on the telephone recently, a separate market may develop for homocysteine as a marker for the development of premature CHD as the result of recent journal articles. The concern for good medical practice that you expressed regarding possible misinterpretation based on only partial metabolite data is well taken.

If we are to offer homocysteine as a single test, it may be advisable to have a canned comment appear on the patient report indicating test limitations and suggesting possible followup testing. With that in mind, the following comment is for your perusal.

> **NOTE: Moderately high levels of serum homocysteine are associated with subsequent risk of myocardial infarction independent of other coronary risk factors.[1] If, however, the test was ordered to evaluate**

any unexplained hematologic abnormality, a normal or abnormal result is not conclusive, and it is recommended to order the complete Megaloblastic Anemia Profile #706960.

[1]Stampfer, MJ, et al, A Prospective Study of Plasma Homocysteine and Risk of Myocardial Infarction in US Physicians, JAMA, 1992; 268:877-881.

I would appreciate your comments on this and any other suggestions for promoting this test.

Thanks for your assistance.

Sincerely,

/s/_____
Peter W. Wentz, PhD
Director of Toxicology

Plaintiffs' Exhibit 159

Laboratory Corporation of America Holdings
231 Maple Avenue
Burlington. North Carolina 27215
Telephone: 1-800-222-7566, ext. 4176
FAX: 910-222-1568

November 2, 1998

Dr. Robert H. Allen
Metabolite Laboratories, Inc.
301 Garfield St., Unit 2-West
Denver, CO 80206

Re: Royalty Agreement Dated January 31, 1991

Dear Dr. Allen:

Attached is the calculation for the 3rd quarter 1998 BDS payment. Test number 706994 (homocysteine) has been removed for August 1998 and September 1998. This is due to a change in methodology in performing this test. Also, the payment has been reduced for an overpayment for this same test number for August on the LCBS.

I hope the schedule is clear so you can see the earnings from 3rd quarter BDS and the recoupment of the August 1998 LCBS.

If you have any questions, please give me a call.

Sincerely,

/s/ Denise A. Hodge
Denise A. Hodge
Revenue Reporting

Plaintiffs' Exhibit 165A

TIME. 0000 VOL 0000
DOB:
00/00/00
FASTING:
000-000-0000

TESTING N 000/00

LABORATORY CORP
OF AMERICA

[PATIENT NAME]
[PATIENT ADDRESS]
[PATIENT ADDRESS]

05/19/99

HOMOCYST(E)INE, PLASMA/SERUM

Homocyst(e)ine, P/S	–	16.0 HI mcmol/L	5.0 – 15.0 BN

This test is intended to be used as an independent risk factor for vascular disease and is NOT intended for the diagnosis of folate or vitamin B12 deficiency. LabCorp has available the Megaloblastic Anemia Profile, Serum for that purpose.

Homocyst(e)ine Reference Ranges

Normal:	5 – 15
Desirable:	<10

LAB: BRN LABCORP BURLINGTON DIRECTOR: Frank Hancock MD
1447 YORK COURT BURLINGTON NC 27218-2230
BRANCH PHONE: 800-762-4344 LAB PHONE: 336-584-5171

LAST PAGE OF REPORT

Plaintiffs' Exhibit 178

THE HEART REVOLUTION

The Extraordinary Discovery That Finally Laid the Cholesterol Myth to Rest and Put Good Food Back on the Table

Kilmer McCully, M.D.
and Martha McCully

HarperPerennial
A Division of HarperCollins *Publishers*

[1999]

* * * *

The Heart of the Theory

In 1969 I first proposed the homocysteine theory of heart disease. When there is too much homocysteine in the blood, arteries are damaged and plaques form. The result is arteriosclerosis and heart disease. This happens when we don't get enough of certain vitamins—namely B6, B12, and folic acid. These B vitamins are missing in our diets because processing and refining foods (think white flour, sugar, and canning) destroys these sensitive vitamins.

When I first started my research, homocysteine was an obscure minor amino acid known only to biochemists for its function in protein metabolism. Before the disease homocystinuria was discovered to 1962, medical scientists had no clue that homocysteine could be a key player in the most important disease in the population—arteriosclerosis.

Of course, besides diet there are many other factors that can increase homocysteine in our blood: genetic background, certain drugs, aging, hormonal changes such as menopause, smoking, how little we exercise, diabetes, and

high blood pressure. We can't control all these things. But we can do something about our diet, and our diet is the one sure way to keep homocysteine levels low.

How do you eat? Is your diet mostly meat and potatoes? Is it low-fat and high-carbohydrate? Are you a vegetarian? A vegan? Do you follow a high-protein plan? How you eat affects how your body prevents disease.

Often it's the balance of what you eat that needs adjustment. For example, an amino acid called methionine is one of the essential building blocks of all proteins in foods. It is especially abundant in meats and dairy products. In the body, methionine is normally converted to homocysteine. We need some methionine, but an excessive amount will create too much homocysteine, damaging the arteries. The good news is that homocysteine can also be converted back to methionine or excreted from the body by the three

* * * *

Proof of the Homocysteine Theory

In the 1990s the results of some very important studies proving the homocysteine theory were discussed in the national media. Unlike the cholesterol hypothesis, the homocysteine theory has been proven by experimental studies with animals, studies of homocysteine levels in patients with heart disease and stroke, and studies of populations that are susceptible to arteriosclerosis. As discussed previously, the arteriosclerosis produced in monkeys fed a diet deficient in vitamin B6 was interpreted as the result of increased blood homocysteine levels. To test this interpretation, homocysteine was infected into rabbits, baboons, and other animals. Just as predicted, these experiments show that homocysteine causes plaques to form in arteries and blood clots within veins and arteries. Plaques are a thickening on the artery wall caused by an overgrowth of muscle cells and deposits of fibrous tissue. What role does homocysteine play? Homocysteine affects this process in several ways. It damages the cells lining the artery walls, stimulating over growth of muscle cells. Homocysteine also releases a substance that destroys the elastic tissue of the artery. The

final result is a thickened, tough, inelastic artery wall. With time, the plaques develop calcium deposits. The experiments also clearly show that the fats and cholesterol within plaques are a complication, not a cause, of arteriosclerosis. If butter or cholesterol is given to animals that are infected with homocysteine, the plaques in the arteries will contain deposits of fats and cholesterol. However, the fats and cholesterol are not *causing* the damage, they are only being deposited where damage has already occurred. If no fat or cholesterol is added to the diet, the plaques don't contain fat or cholesterol, but the plaques are destructive nonetheless since they narrow the arteries.

Of course, the most powerful proof is in human studies. Some 10-40 percent of patients with vascular disease in clinics and hospitals worldwide has consistently been shown to have high levels of homocysteine. Up to two-thirds of the elderly are deficient in either B6, B12, or folic acid, as shown by the Framingham Heart Study. Patients with deficiencies of folic acid have high levels of homocysteine in their blood all the time. Others with a deficiency of B6 will only have large increases in homocysteine in their blood within a few hours after meals. If a person is deficient in folic acid *and* vitamin B6, blood homocysteine will be elevated both before and after meals. Studies have shown that folic acid keeps blood homocysteine levels low by converting it back into methionine. Vitamin B6 turns homocysteine into other substances that are excreted from the body in the urine.

Here are some examples of the large-scale population studies definitively showing that elevation of blood homocysteine is associated with increased risk of heart attack and heart disease.

- In February 1998 investigators at the Harvard School of Public Health published the results of the Nurses' Health Study, one of the studies that originally set out to prove that cholesterol was causing heart disease. Instead this study has shown that deficiencies of B vitamins are doing the damage. During a fourteen-year period, 80,000 participants answered question-

naires about their food consumption. The study revealed that those nurses with the lowest consumption of folic acid and B6 had the highest death rates from cardiovascular disease and heart attack.

- In April 1998 investigators from England published a study of 21,500 men who were followed for almost nine years. Blood homocysteine levels were higher in men who died of heart disease than in men who did not. The higher the blood homocysteine level, the higher the risk of dying from heart disease.

- The Physicians Health Study, completed in 1992, showed that among the 14,000 participants, those with high homocysteine were three times more likely to have a heart attack during a five-year period than persons with normal levels.

- In the 1996 Nutrition Canada Study of 5,000 people studied for fourteen years, those with the lowest levels of folic acid in the blood were almost twice as likely to die from heart disease as those with the highest levels.

- A study from Norway showed that among 587 patients with proven coronary heart disease, risk of death is directly related to the level of homocysteine in the blood. Cholesterol level, on the other hand, did not predict the risk of death.

- The Hordaland Study of 16,000 residents of Bergen, Norway, showed that homocysteine increases in the presence of other known risk factors for heart disease, including male gender, old age, smoking, high blood pressure, elevated cholesterol level, and lack of exercise.

- A multicountry study in 1997 showed that the death rate from coronary heart disease is directly related to blood homocysteine levels. In northern European countries, where heart disease is frequent, people have higher blood levels of homocysteine than in southern

European countries, where heart disease is less frequent.

The study in Hordaland, Norway, is especially interesting because a variety of factors associated with heart disease were related to high blood homocysteine. Known risk factors for heart disease—aging, male gender, menopause, lack of vegetables and fruits or vitamin supplements, lack of exercise, high blood pressure, and smoking—cause homocysteine levels to rise. The studies from Canada and the Nurses Health Study show directly that death from heart disease is related to dietary deficiencies of folic acid and vitamin B6. The Physicians Health Study and the British study show that elevated blood homocysteine increases the risk of dying from heart disease. All these studies are powerful evidence supporting the validity of the homocysteine theory of heart disease,

There are, in fact, many cases of heart disease in which cholesterol levels are quite normal. Usually these patients have high homocysteine that is independent of cholesterol; remember J.E. from the first case study. In 1990 a study at the Providence V.A. Medical Center showed that the patients with the most advanced arteriosclerosis typically had normal cholesterol levels, and two-thirds of all these patients had no hypertension, diabetes, or elevated cholesterol at all. Only about 15 percent of cases with severe arteriosclerosis had high cholesterol. Eating a cholesterol-rich diet doesn't cause heart disease, and measuring blood levels of cholesterol fails to predict heart disease in most of those who have it.

Another significant factor can affect homocysteine levels. About 12 percent of the population worldwide carry a genetic defect affecting the ability to metabolize homocysteine normally. All of us have an enzyme, methylenetetrahydrofolate reductase, that combines with folic acid to lower homocysteine levels. People born with an abnormality of this enzyme need to consume even more folic acid than normal to keep homocysteine levels in check. If folic acid intake is deficient, people with this

genetic defect have a greater chance than average of developing arteriosclerosis and heart disease because of elevated homocysteine levels. If you have a strong family history of heart disease, it is worth checking to find out if you have this enzyme abnormality. Specialized biochemical and genetic tests available in commercial laboratories and medical centers can detect this abnormality. I'll talk about how much folic acid you should take in Chapter Five.

An Action Plan: Prevention and Therapy of Heart Disease

Now we know what causes heart disease, and how homocysteine works. We even know what can be done to lower homocysteine levels, which you'll learn throughout this book. And it's not just for prevention. If you already have heart disease, vitamin therapy can lower homocysteine and stop the disease from progressing. A 1998 clinical study from Canada offers the first proof that B vitamin therapy can prevent arteriosclerosis from getting worse. Patients with elevated homocysteine and arteriosclerosis of arteries to the brain were given intensive therapy with folic acid, vitamin B6, and vitamin B12. The plaques stopped progressing and the homocysteine levels returned to normal. In a 1996 study of patients with coronary heart disease, therapy with vitamin B6, folic acid, B12, and other nutrients slowed the development of the disease.

The amount of these vitamins needed to keep homocysteine in check (3 milligrams of B6 and 400 micrograms of folic acid) is provided by the Heart Revolution diet. Luckily, homocysteine levels can be lowered simply and safely by using B vitamins. And it's never too late to start. We knew B vitamins were important before these studies, but now we understand *why* they are so vital.

In 1995 a group of patients being treated for carpal tunnel syndrome ended up reaping the benefits of the homocysteine approach. This common painful condition is caused by overuse of the wrist, hand, and fingers

(typists and tennis players are typical sufferers). In other cases the condition is related to pregnancy, diabetes, or hormonal disturbances. Patients were given large doses of B6 to alleviate the symptoms. Most of these patients were helped, but the study also revealed that these patients had a far lower incidence of heart disease than would have been expected. In addition, the study found that many of these patients were originally deficient in vitamin B6 in the blood, which for many had produced symptoms of heart disease as well as carpal tunnel syndrome.

All of these examples point to the key role B vitamins play in the health of the body. But the purpose here is to make sure you get enough of them in your diet to prevent heart disease. In the next several chapters you'll see how the American diet has failed to provide adequate nutrients. You'll also read about ways to improve your diet so that you can protect yourself.

The American public is ready for a revolutionary way of thinking. Once we change our ideas about what causes heart disease, we can improve our diets, prevent disease, and live the healthier life that is within our grasp.

Plaintiffs' Exhibit 180

Homocyst(e)ine *The Bad Amino Acid?*

By Peter W. Wentz, PhD

[1999]

Introduction

The pioneering work of Dr. Kilmer McCully has led to the development of the homocyst(e)ine theory of arteriosclerosis. The theory accounts for many of the causes of severe arteriosclerosis in patients with lifelong normal or desirable cholesterol levels (<200 mg/dL). It is estimated that an elevated blood homocyst(e)ine level may account for at least 10 percent of the risk of coronary heart disease in the U.S. population.

Cross-sectional, epidemiological and case-control studies have confirmed the relationship between elevated homocyst(e)ine levels and the risk of atherosclerotic disease. No causal relationship has been established, but studies are under way to determine whether lowering homocyst(e)ine will prevent occlusion in patients at risk for cardiovascular, cerebrovascular and peripheral vascular disease.

Atherogenic Effect of Homocyst(e)ine

According to the homocyst(e)ine theory, the origin of arteriosclerosis is the toxic effect of homocyst(e)ine on the endothelial lining of arteries, which causes plaque formation. Evidence for this has come from in vitro studies in human cell cultures and from in vivo animal models. The mechanism of action is unclear but may be related to the formation of LDL- homocyst(e)ine aggregates, which are taken up by macrophages of the artery wall to form the foam cells of early arteriosclerotic plaques. For a recent review of the hypothesized mechanisms of blood vessel injury, refer to the published proceedings of the 1998 Beckman Conference.

What is Homocyst(e)ine?

Homocyst(e)ine, a thiol-containing amino acid, has the empirical formula $SHCH_2CH_2(NH_2)COOH$ and a molecular weight of 135.2. In vivo, the reactive sulfhydryl group (-SH) of homocyst(e)ine combines with the sulfhydryl group of cysteine to form a mixed disulfide and with the cysteine residues in proteins to form stable disulfide bonds. The auto-oxidized, dimeric form of homocyst(e)ine is referred to as homocystine. In the circulation, more than 90 percent of homocyst(e)ine is present in combination with plasma proteins, primarily albumin. Collectively, the sum of these species is referred to as total homocyst(e)ine and abbreviated tHcy.

Screening for Homocystinuria

Plasma homocystine measurements have been used to screen newborns for homocystinuria, an inborn error of homocyst(e)ine metabolism characterized by a marked increase in the concentrations of plasma and urinary tHcy. Homocystine, however, is unstable in plasma processed at room temperature and is rapidly converted to the more stable protein-bound forms. In vitro, deproteinization of plasma or serum must be done immediately after blood collection to detect free homocystine or the mixed disulfides in the supernatant fluid. Plasma or serum collected at room temperature with no deproteinization step is comprised entirely of protein-bound homocyst(e)ine. Using homocystine as a marker, a missed diagnosis of homocystinuria can result if deproteinization is not performed immediately.

The most effective screening method for diagnosis of homocystinuria is the measurement of total homocyst(e)ine in serum or plasma. In vitro, total homocyst(e)ine is stable with no special specimen preparation required, thereby avoiding the missed diagnosis of homocystinuria associated with a false-negative homocystine result. It is a matter of practical consideration that in the analytical measurement of tHcy, the initial step actually involves the reduction of all disulfide bonds to yield the free, reduced form of homocyst(e)ine.

Source of Homocyst(e)ine in Humans

Homocyst(e)ine is produced in the liver exclusively from the demethylation of dietary methionine, an essential amino acid found in red meats and dairy products. Unlike cholesterol, no homocyst(e)ine is produced in vivo starting with 2-carbon moieties. The interconversion of methionine and homocysteine depends on the availability of the methyl donor 5-methyltetrahydrofolate, cofactors vitamin B_{12} and folate, and the enzyme activity of methionine synthase.

How is Homocyst(e)ine Metabolized?

After homocyst(e)ine is derived from methionine, it undergoes either remethylation to methionine or is metabolized all the way to sulfate via the intermediary compounds cystathionine and cysteine. Several B-complex vitamins serve as cofactors and substrates in the metabolism of methionine and homocyst(e)ine (Fig. 1). Folic acid and vitamin B_{12} (cyanocobalamin) regulate metabolic pathways catalyzed by the enzymes methylenetetrahydrofolate reductase (MTHFR) and methionine synthase, whereas vitamin B_6 (pyridoxal phosphate) is a cofactor for cystathionine B-synthase (CBS). The latter route is referred to as the transsulfuration pathway. Individuals heterozygous for CBS deficiency are predisposed to hyperhomocyst(e)inemia and, although having a normal basal level of homocyst(e)ine, can be identified by the methionine loading test.

What is a Normal Homocyst(e)ine Level?

Using any of the standard analytical methods, values between 5 and 15 µmol/L are generally considered normal, albeit not optimal or desirable. Levels tend to increase with age and pre-menopausal women younger than 65 have lower values than men in the same age bracket. After menopause, women have comparable levels to men. Values <10 µmol/L may be considered desirable, values <12 µmol/L optimal, and values 12 to 15 µmol/L borderline. Moderate hyperhomocyst(e)inemia is defined as >15 to 30 µmol/L, intermediate as >30 to 100 µmol/L and severe as >100 µmol/L.

What is the Relative Risk for Coronary Artery Disease (CAD)?

Based on case data for 130 patients hospitalized with their first acute myocardial infarction (AMI) and 118 population controls, an odds ratio of 1.35 for each 3.0 µmol/L increase in homocyst(e)ine above 7.2 µmol/L can be used to calculate a relative risk for occlusive vascular disease. The calculation is:

$$\text{Risk of MI} = \frac{\text{tHcy} - 7.2}{3} \times 035 + 1.00$$

This study shows that even optimal levels of homocyst(e)ine (i.e., <12 µmol/L) pose an increased risk for arteriosclerosis compared with the lowest 20th percentile (<7.2 µmol/L) for population controls.

In another study involving 587 patients with confirmed CAD, Nygärd et al found a strong relationship between homocyst(e)ine levels and cardiovascular mortality rates. After 4.6 years, using 9.0 µmol/L as a reference point, the mortality rate increased 1.9-, 2.8- and 4.5-fold among patients with tHcy levels of 9.0-14.9, 15.0-19.9 and ≥ 20.0 µmol/L, respectively. This translates into a death rate of 3.6 percent for patients with a tHcy level <9.0 µmol/L compared with a mortality of 24.7 percent for those with levels >14.9 µmol/L.

Using homocyst(e)ine levels of <10 and >15 to compare relative risk for CAD mortality, Omenn et al suggested that the risk differential is comparable to that between total serum cholesterol levels of 189 and 275 mg/dL.

* * * *

How Can Folate Deficiency be Differentiated From Vitamin B_{12} Deficiency?

For subclinical vitamin deficiencies, where vitamin B_{12} and/or folate levels are normal or borderline low, a comprehensive metabolite profile has the highest diagnostic sensitivity for identifying patients at risk and for differentiating between suboptimal folate and vitamin B_{12} status. A mega-

loblastic anemia profile consists of homocysteine, cystationine, methylmalonic acid and 2-methylcitrate.

In cobalamin deficiency, all four parameters are elevated, but in folate deficiency, typically only homocysteine and cystathionine are increased. Most importantly, elevated levels of these metabolites will correct to normal after treatment with the appropriate vitamin, but will not normalize after treatment with the wrong vitamin, even in pharmacological amounts. Serum metabolite levels can be rechecked five to 15 days after vitamin therapy is initiated.

* * * *

Summary

Homocyst(e)ine has been shown to be an independent risk factor for the development of atherosclerotic vascular disease. Acquired forms of hyperhomocyst(e)inemia are due to vitamin deficiencies and exposure to drugs and toxins. Familial homocystinuria is a homozygous expression of enzyme defects or deficiencies involving the Hcy metabolizing pathways.

The most important determinants of tHcy have been identified as age and sex, folate and vitamin B_{12} status, and renal function. Vitamin supplementation, especially folic acid, is effective at lowering blood tHcy levels. High-risk patients, refractory to high-dose vitamin therapy, may benefit from tHcy-lowering drugs.

Normal levels of homocyst(e)ine are 5 µmol/L to 15 µmol/L Optimal levels, cautiously defined as <12 µmol/L, still pose some cardiovascular risk. Prevention programs target the lowering of tHcy levels to <10 µmol/L. The Nutrition Committee of the American Heart Association states: "A basal homocyst(e)ine level <10 µmol/L is a reasonable therapeutic goal for subjects at increased risk, defined as those patients with personal or family history of premature cardiovascular disease, as well as those with malnutrition, malabsorption syndromes, hypothyroidism, renal failure, systemic lupus erythematosus; those taking certain medications, eg, nicotinic add, theophylline, bile acid-

binding resins, methotrexate, and L-dopa: or those with recent nitrous oxide exposure.

It remains to be demonstrated in placebo-controlled multi-center clinical trials that a reduction of tHcy will lower morbidity and mortality both in patients with vascular disease and in the general population.

* * * *

Plaintiffs' Exhibit 181

Megaloblastic Anemia Profiles:
Laboratory Screening and Confirmation

By Peter W. Wentz, PhD, DABCC

[1999]

* * * *

MEGALOBLASTIC ANEMIA PROFILE

The megaloblastic anemia profile is comprised of methylmalonic acid, 2-methylcitrate, homocysteine and cystathionine. All four metabolites are elevated in most patients with cobalamin deficiency, whereas only homocysteine and cystathionine are elevated in most patients with folate deficiency.

- *Methylmalonic Acid (MMA).* The serum methylmalonic acid level is elevated in more than 95 percent of patients with clinically confirmed cobalamin deficiency. Values as high as 200,000 nmol/L have been observed, with a median value in the range of 3,500 nmol/L. Frequently an elevated serum MMA is seen before a low cobalamin develops in patients with pernicious anemia in remission, when maintenance vitamin B_{12} injections are missed for several months.

The cutoff for MMA is set at +3sd above the mean for healthy blood bank donors. This level provides greater specificity for the diagnosis of cobalamin deficiency despite the loss of some sensitivity. For a confirmatory test, the highest diagnostic specificity is desirable. Moelby et al have concluded that serum methylmalonic acid is a sensitive and probably specific indicator of cobalamin deficiency, having a diagnostic efficiency of 95 percent.

Note that elevations of serum methylmalonic acid due to cobalamin deficiency do not respond to pharmacologic doses of folate. Using MMA value of >375 nmol/L as the reference standard for cobalamin deficiency, Holleland et al have

determined a diagnostic sensitivity of 40 percent and a diagnostic specificity of 98 percent for the serum cobalamin assay (cutoff of 230 pg/mL).

- *Homocysteine (HCy).* An elevated serum homocysteine level is a marker for both cobalamin and folate deficiencies. Values as high as 500 µmol/L have been observed in cobalamin deficiency, with a median of 70 µmol/L. In folate deficiency, folate values may be as high as 250 µmol/L, with a median of 50 µmol/L. Elevations of homocysteine due to folate deficiency do not respond to pharmacologic doses of cobalamin.

- *2-Methylcitrate.* Increased levels of propionyl-CoA lead to increased synthesis of 2-methylcitric acid by citrate synthase (Fig. 3), which usually uses acetyl-CoA instead of propionyl-CoA to form citric acid. In cobalamin deficiency, 2-methylcitrate values may be as high as 15,000 nmol/L. Serum levels of 2-methylcitrate are elevated in more than 85 percent of patients with clinically confirmed cobalamin deficiency. In folate deficiency, 2-methylcitrate is usually normal.

- *Cystathionine.* Homocysteine is metabolized to cystationine by the transsulfuration pathway (Fig. 2b) and in cases of cobalamin deficiency cystathionine values may be as high as 4,000 nmol/L. In folate deficiency, levels may be as high as 18,000 nmol/L. Cystationine is shown to be elevated in 87 percent and 95 percent of patients with cobalamin and folate deficiency, respectively.

Serum levels of these metabolites are useful in diagnosing and distinguishing between cobalamin and folate deficiency. Savage et al concluded that normal levels of both methylmalonic acid and homocysteine rule out clinically significant cobalamin deficiency with virtual certainty. Furthermore, an elevated methylmalonic acid (or both MMA and Hcy) is much more specific for cobalamin deficiency than is a low cobalamin level, which is frequently seen without any other clinical evidence of deficiency. The only significant limitation to the specificity of an elevated MMA or a combined elevated MMA/Hcy is underlying renal insufficiency or

volume depletion, which may falsely elevate both metabolites.

Statistically, both MMA and Hcy are elevated in approximately 98 percent of cobalamin-deficient patients with megaloblastic anemia, whereas methylmalonic acid is more often elevated than homocysteine in non-anemic patients. Nevertheless, methylmalonic acid was normal in seven of 434 episodes of cobalamin deficiency, although homocysteine was elevated in six of the seven episodes. They recommend combining the two metabolite determinations to improve the rate of correctly diagnosing cobalamin deficiency over that of methylmalonic acid alone.

In this same study. Savage et al found an elevated homocysteine in 97.5 percent of 121 episodes of folate deficiency, compared with only a 12.4 percent (15/121) incidence of elevated methylmalonic acid. Fourteen out of 15 patients with elevated methylmalonic acids had renal dysfunction. The one exception could not be explained and is presumably a false-positive result.

When used together with serum levels of cobalamin and folate, it's possible to diagnose and distinguish between cobalamin and folate deficiency in the vast majority of patients. The combined approach to diagnosis is important because approximately 5 percent of patients with clinically confirmed cobalamin or folate deficiency will have normal serum metabolite levels, and as many as 10 percent will have values for serum cobalamin and folate that are well within the normal range.

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Plaintiffs' Exhibit 182

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Health Care Providers

About LabCorp

LabCorp is one of the largest clinical laboratory networks in the United States, with service extended to more than 100,000 clients in 49 states. Through a comprehensive menu of clinical test options, from the clinical chemistry to sophisticated technologies such as polymerase chain reaction (PCR) and DNA probe analyses, LabCorp assists physicians and other health care practitioners in the diagnosis, treatment, and monitoring of their patients.

About this site

LabCorp regularly publishes literature on several areas of clinical laboratory testing. This website is designed to enable health care providers to find the information they need to better serve their patients. The section is divided into two subsections, with applicable subtopics for each, as listed below.

Medical Specialties

- Allergy
- Cardiology
- Endocrinology
- Gastroenterology
- Geriatrics
- Infectious Disease
- Nephrology
- Oncology
- Pulmonology
- Rheumatology

Surgical Specialties

- Obstetrics/Gynecology
- Orthopaedics
- Urology

Select the appropriate link below for access to specialized LabCorp publications as well as links to other informative sites. Publications, links, and other communications found on this site are not intended as a substitute for consultation with an appropriate technical expert.

Medical Specialties Surgical Specialties
Patient Service Centers Locator

LabCorp®
358 South Main Street
Burlington, NC 27215
336-222-7566

8/14/01

Plaintiffs' Exhibit 183

Homocyst(e)ine, Plasma or Serum (706994)

CPT 82131

Related Information

- Anemia Profile, Megaloblastic, Serum

* * * *

Reference Interval

Homocyst(e)ine:

- Normal: 5-15 µmol/L
- Optimal: <12 µmol/L

Hyperhomocyst(e)inemia:

- Borderline: 12-15 µmol/L
- Moderate: >15-30 µmol/L
- Intermediate: >30-100 µmol/L
- Severe: >100 µmol/L

* * * *

Studies have shown that even optimal levels of homocyst(e)ine pose an increased risk for arteriosclerosis compared with the lowest 20th percentile (<7.2 µmol/L) of population controls.

Use: Evaluate borderline folate deficiency as a part of Anemia Profile, Megaloblastic, Serum (test 706960). Homocysteine has been shown to be an independent risk factor for the premature development of coronary artery disease and thrombosis.

* * * *

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Plaintiffs' Exhibit 184

Anemia Profile, Megaloblastic, Serum (706960)

* * * *

Reference Interval See table.

Megaloblastic Anemia Profile, Serum

Serum Metabolite	Normal Range	% High Values	B_{12} Deficiency Range	% High Values	Folate Deficiency Range	% High Values
Methylmalonic acid	73-271	<3	272-200,000	>95	73-271 nmol/L	<3
2-Methylcitric acid	60-228	<3	228-15,000	>80	60-228 nmol/L	<3
Homocysteine	5.1-13.9	<3	14-500	>95	14-250 µmol/L	>95
Cystathionine	44-342	<3	342-4000	>80	342-18,000 nmol/L	>80

Serum methylmalonic acid and homocysteine are the primary metabolic tests for diagnosing and distinguishing between B_{12} and folate deficiency. They can be used in conjunction with the serum B_{12}, which is usually low or low normal (<350 pg/mL) in B_{12} deficiency, and the serum folate, which is usually low or low normal (<5mg/mL) in folate deficiency. 2-Methylcitric acid and cystathionine provide confirmatory evidence for such deficiencies. Homocysteine and especially cystathionine may also be high in B_6 deficiency.

Elevated levels of serum metabolites will correct to normal after treatment with the appropriate vitamin but will not correct after treatment with the wrong vitamin, even in pharmacologic amounts.

* * * *

Additional Information The megaloblastic anemia profile monitors four compounds: methylmalonic acid, 2-methylcitric acid, homocysteine, and cystathionine. It has been shown that all four of these compounds are elevated if a

patient is suffering from vitamin B_{12} deficiency (megaloblastic anemia, cobalamin deficiency) and that homocysteine and cystathionine are elevated if there is a folic acid deficiency. Methylmalonic acid and homocysteine are the primary tests for diagnosis. 2-Methylcitric acid and cystathionine provide confirmatory information.

This method is a more specific diagnostic tool for B_{12} and folate deficiencies as it has been shown that some patients with deficiencies will have normal or borderline serum B_{12} or folate. These deficiencies can lead to incapacitating and life-threatening neuropsychiatric abnormalities which are completely reversible by treatment with B_{12} or folic acid. As with any such condition early detection is very important. This profile provides early detection and differentiation. This differentiation is very important because both B_{12} and folate deficiencies have indistinguishable hematological abnormalities. The greatest improvement is observed when the proper vitamin is used and only B_{12} will correct the neuropsychiatric abnormalities seen in cobalamin deficiency. There is also recent literature linking cardiovascular disease with homocysteine elevation.

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tx008700.htm 7/19/99

Plaintiffs' Exhibit 185

Total Homocysteine in Plasma or Serum: Methods and Clinical Applications

Clinical Chemistry, Vol. 39, No. 9, [1764-1779]

1993

Per M. Ueland,[1,5] Helga Refsum,[1] Sally P. Stabler,[2] M. Rene Malinow,[3] Anders Andersson,[4] and Robert H. Allen[2]

Total homocysteine is defined as the sum of all homocysteine species in plasma/serum, including free and protein-bound forms. In the present review, we compare and evaluate several techniques for the determination of total homocysteine. Because these assays include the conversion of all forms into a single species by reduction, the redistribution between free and protein-bound homocysteine through disulfide interchange does not affect the results, and total homocysteine can be measured in stored samples.

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Reduction. Determination of total Hcy in plasma/serum requires the reduction of the disulfide bond between Hcy and other thiols or albumin.

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Plaintiffs' Exhibit 194

LabCorp Directory of Services & Interpretive Guide [1999]

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ANEMIA PROFILE, MEGALOBLASTIC, SERUM 706960

CPT 82131 (x4)

Related Information

Methylmalonic Acid, Serum *on page 290*
Methylmalonic Acid, Urine *on page 290*
Vitamin B_{12} *on page 385*

Synonyms Megaloblastic Anemia, Serum

Test Includes Cystathionine; homocysteine; 2-methylcitric acid; methylmalonic acid

Specimen Serum or plasma

Volume 2.2 mL

Minimum Volume 1.1 mL

Container Red stopper tube or serum-separator tube or green-stopper (heparin plasma) tube

Collection Separate serum or plasma from cells within 1 hour of collection and transfer to plastic transport tube.

Storage Instructions Refrigerate

Causes for Rejection Specimen received not separated from cells, plasma from a light blue-stoppered or yellow-stoppered tube; citrate interferes with assay; homocysteine results increase by approximately 35% and 75% for specimens not centrifuged and/or not separated from the clot for periods of 4 and 24 hours respectively

Reference Interval See table

Megaloblastic Anemia Profile, Serum

Serum Metabolite	Normal Range	% High Values	B_{12} Deficiency Range	% High Values	Folate Deficiency Range	% High Values
Methylmalonic acid	73-271	<3	272-200,000	>95	73-271 nmol/L	<3
2-Methylcitric acid	80-228	<3	228-15,000	>90	60-228 nmol/L	<3
Homocysteine	51-139	<3	14-500	>95	14-250 µmol/L	>95
Cystathionine	44-342	<3	342-4000	>80	342-18,000 nmol/L	>80

Serum methylmalonic acid and homocysteine are the primary metabolic tests for diagnosing and distinguishing between B_{12} and folate deficiency. They can be used in conjunction with the serum B_{12}, which is usually low or low normal (<350 pg/mL) in B_{12} deficiency, and the serum folate, which is usually low or low normal (<5 mg/mL) in folate deficiency. 2-Methylcitric acid and cystathionine provide confirmatory evidence for such deficiencies. Homocysteine and especially cystathionine may also be high in B_{12} deficiency.

Elevated levels of serum metabolites will correct to normal after treatment with the appropriate vitamin but will not correct after treatment with the wrong vitamin, even in pharmacologic amounts.

Any of the four metabolites can be elevated due to renal insufficiency or intravascular volume depletion. This occurs most commonly in the case of 2-methylcitric acid and cystathionine. Elevated metabolite levels do not correct with B_{12}, folate or B_6 treatment unless vitamin deficiency coexists.

Serum metabolite levels can be rechecked 5-15 days after vitamin therapy.

Normal ranges 6 hours postoral methionine load (100 mg L-methionine/kg body weight) are as follows: homocysteine 16.5-45.7 µmol/L and cystathionine: 424-2500 nmol/L. Methylmalonic acid and 2-methylcitric acid do not change after a methionine load.

Use Diagnose megaloblastic anemia. Elevated levels of methylmalonic acid provide an early indication of cobalamin (B_{12}) deficiency.

Methodology–Gas chromatography/mass spectrometry (GC/MS)

Additional Information The megaloblastic anemia profile monitors four compounds: methylmalonic acid, 2-methylcitric acid, homocysteine, and cystathionine. It has been shown that all four of these compounds are elevated if a patient is suffering from vitamin B_{12} deficiency (megaloblastic anemia, cobalamin deficiency) and that homocysteine and cystathionine are elevated if there is a folic acid deficiency. Methylmalonic acid and homocysteine are the primary tests for diagnosis. 2-Methylcitric acid and cystathionine provide confirmatory information.

This method is a more specific diagnostic tool for B_{12} and folate deficiencies as it has been shown that some patients with deficiencies will have normal or borderline serum B_{12} or folate. These deficiencies can lead to incapacitating and life-threatening neuropsychiatric abnormalities which are completely reversible by treatment with B_{12} or folic acid. As with any such condition early detection is very important. This profile provides early detection and differentiation. This differentiation is very important because both B_{12} and folate deficiencies have indistinguishable hematological abnormalities. The greatest improvement is observed when the proper vitamin is used and only B_{12} will correct the neuropsychiatric abnormalities seen in cobalamin deficiency. There is also recent literature linking cardiovascular disease with homocysteine elevation.

* * * *

HOMOCYST(E)INE, PLASMA OR SERUM 706994

CPT 82131

Related Information

Anemia Profile, Megaloblastic Serum *on page 114*

Specimen Plasma or serum

Volume 2.2 mL

Minimum Volume 1.1 mL

Container Lavender-stopper (EDTA) tube or red-stopper tube or serum-separator tube or green-stopper (heparinized plasma) tube.

Collection Separate plasma or serum from cells within 1 hour of collection and transfer to plastic transport tube

Storage Instructions Refrigerate

Patient Preparation A fasting specimen is preferred to establish baseline values or monitor treatment.

Causes for Rejection Specimen received not separated from cells; plasma from a light blue-stopper or yellow-stopper tube; citrate interferes with assay. Homocysteine results increase by approximately 35% and 75% for specimens not centrifuged and/or not separated from the clot for periods of 4 and 24 hours, respectively.

Reference Interval

Homocyst(e)ine:

- Normal: 5-15 µmol/L
- Optimal: < 12 µmol/L

Hyperhomocyst(e)inemia:

- Borderline: 12-15 µmol/L
- Moderate: > 15-30 µmol/L
- Severe > 100 µmol/L

Detection limit: 2.5 µmol/L

Studies have shown that even optimal levels of homocysteine pose an increased risk for arteriosclerosis compared with the lowest 20th percentile (< 7.2 µmol/L) of population controls.

Use Evaluate borderline folate deficiency as a part of Anemia Profile. Megaloblastic Serum (test 706960) Homocysteine has been shown to be an independent risk factor for the premature development of coronary artery disease and thrombosis.

Methodology Immunoassay

* * * *

Plaintiffs' Exhibit 195

LabCorp Directory of Services & Interpretive Guide

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HOMOCYST(E)INE, PLASMA OR SERUM 706994

CPT 82131

Specimen Plasma or serum.

Volume 1 mL

Minimum Volume 0.3 mL

Container Lavender-stopper (EDTA) tube or red-stopper tube or serum-separator tube or green-stopper (heparinized plasma) tube

Collection EDTA plasma is the preferred specimen. Separate plasma from cells immediately to avoid a false elevation of homocysteine. After 1 hour at room temperature, a 10% increase may be seen. Transfer plasma or serum to a plastic transport tube.

Storage Instructions Refrigerate

Patient Preparation A fasting specimen is preferred to establish baseline values or monitor treatment.

Causes for Rejection Specimen received not separated from cells; plasma from a light blue-stopper or yellow-stopper tube; citrate interferes with assay. Homocysteine results increase by approximately 35% and 75% for specimens not centrifuged and/or not separated from the clot for periods of 4 and 24 hours, respectively.

Reference Interval

Homocyst(e)ine:

- normal: 5-15 µmol/L
- desirable: < 10 µmol/L

Hyperhomocyst(e)inemia:

- borderline: 12-15 µmol/L
- moderate: > 15-30 µmol/L
- intermediate: > 30-100 µmol/L
- severe: > 100 µmol/L

Studies have shown that even optimal levels of homocyst(e)ine pose an increased risk for arteriosclerosis compared with the lowest 20th percentile (< 7.2 µmol/L) of population controls.

Use Homocysteine has been shown to be an independent risk factor for the premature development of coronary artery disease and thrombosis. This test is intended for use in screening patients who may be at risk for heart disease and stroke. Evaluate borderline folate deficiency as a part of Anemia Profile, Megaloblastic, Serum (test 706960).

Methodology Immunoassay

* * * *

Plaintiffs' Exhibit 218

From: Peter Wentz -
To: mml@mayo.edu
Date: Thu, Jun 10, 1999 4:13 PM
Subject: Homocysteine, Plasma (#80379)

Dear Sir,

Is this test performed pursuant to a licensing agreement with Competitive Technologies (Patent Number: 4,940,658)? Under Claim 13 of the patent the methodology of the homocysteine assay is unimportant. Claim 13 claims any method for detecting a deficiency of either cobalamin or folate by assaying for homocysteine. Have you been able to successfully challenge this provision? Thanks for the feedback.

Regards,

Peter Wentz

Plaintiffs' Exhibit 278

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLORADO

Civil Action No. 99-Z-870

METABOLITE LABORATORIES, INC.,
a Colorado corporation, and
COMPETITIVE TECHNOLOGIES, INC.,
a Delaware corporation,

Plaintiffs,

vs.

LABORATORY CORPORATION OF AMERICA HOLDINGS d/b/a LabCorp, a Delaware corporation,

Defendant.

STIPULATION

Based upon a review of available data, Plaintiffs Metabolite Laboratories, Inc. ("Metabolite") and Competitive Technologies, Inc. ("CTI") and Defendant Laboratory Corporation of America Holdings d/b/a LabCorp ("LabCorp") hereby stipulate as follows:

1. The total number of single homocysteine tests (Test # 706994) performed by LabCorp using the Abbott method and billed by LabCorp (from August 1, 1998 to September 30, 2001 for the LCBS System, from August 1, 1998 to September 30, 2001 for the BDS System, from August 1, 1998 to October 29, 2001 for the Dallas Lab and from August 1, 1998 to October 31, 2001 for the San Diego Lab) was 351,458 tests.

2. The billed revenues associated with the 351,458 single homocysteine tests (Test #706994) performed by LabCorp

using the Abbott method from August 1, 1998 to the dates indicated in Stipulation No. 1 were $16,989,416.81.

This 13th day of November, 2001.

/s/ J. Gregory Whitehair
Glenn K. Beaton
J. Gregory Whitehair
GIBSON, DUNN
& CRUTCHER LLP
1801 California Street
Suite 4100
Denver, CO 80202-2641
Telephone: (303) 298-5700
Fax: (303) 296-5310
D.C. Box No. 18

Attorney for Plaintiffs

/s/ Dow N. Kirkpatrick II
James A. Jablonski
DC Box-004
GORSUCH KIRGIS, LLP
1515 Arapahoe St.
Tower I
Suite 1000
Denver, CO 80202
Telephone: 303/376-5000

Dow N. Kirkpatrick II
John P. Higgins
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street
Suite 4000
Charlotte, North Carolina
28280
Telephone: 704/444-1000

Attorneys for Defendant
Laboratory Corporation of
America Holdings

Defendant's Exhibit K

[SEAL]

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT		ATTORNEY DOCKET NO.
06/933,553	11/20/86	ALLEN	R	CU280/281

BARBARA A. SHIMEI
UNIVERSITY PATENTS, INC.
P.O. BOX 901
WESTPORT, CT 06881

EXAMINER	
SCHEINER, T	
ART UNIT	PAPER NUMBER
182	4

DATE MAILED

08/01/88

This is a communication from the examiner in charge of your examination.
COMMISSIONER OF PATENTS AND TRADEMARKS

Part II SUMMARY OF ACTION

* * * *

1. ☒ Claims 1-32 are pending in the application.

* * * *

4. ☒ Claims 1-32 are rejected.

* * * *

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

The Abstract is objected to because it should be entitled "Abstract of the Disclosure".

Claims 1-32 are rejected under 35 U.S.C. 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the word "different" is superfluous and should be removed. In step (a), "the" should be replaced with "a", "an known" should be "known".

Claim 2 is vague and indefinite in its recitation of "appropriate derivatives" as no criteria of "appropriateness" are provided.

Claims 6 and 9 are vague and indefinite in their recitations of "partially purifying" since no degree or method of purification is mentioned.

In claim 10, the language "an appropriate non-sulfhydryl amino acid internal. . ." is indefinite, the claim should indicate that the standard is a labeled derivative of the amino acid of interest.

Claim 13 should recite discrete, sequential process steps, for example, obtaining a sample, contacting the sample, etc. The final step should be clearly related to the preamble of the claim.

Claims 13-22 are vague and indefinite in their recitations of "elevated levels" and "normal levels" of total homocysteine. The claims should include quantitative language.

Claim 17 is vague and indefinite in its recitation of "appropriate detection means".

Claim 18 should also recite discrete, sequential process steps, concluding with a step clearly related to the preamble.

The language "and/or" in claims 18 and 19 is confusing. The claims should clearly state each of the possible deficiencies or combinations of deficiencies in the preamble.

Claim 24 is vague and indefinite in its recitation of "appropriate" derivatives.

The language "partially purifying" in claim 28 is indefinite.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-12 are rejected under 35 U.S.C. 103 as being unpatentable over Laseter et al and Freed et al.

Amino acid derivatives, including silyl derivatives, are conventionally determined by mass spectrometry, for an example, see Laseter et al (lines 1-3, and last 5 lines). Further, as shown by Freed et al, the use of radiolabeled derivatives or analogs of compounds of interest as internal reference standards is well known in the art. It would have been obvious for one of ordinary skill in the art to have determined the amount of any particular amino acid or amino acid derivative by mass spectrometry, as taught by Laseter et

al, by combining it with an internal reference standard (a known amount of labeled derivative or analog of the compound of interest) and determining the ratio of labeled to unlabeled compound, as taught by Freed et al.

Claims 13-32 are rejected under 35 U.S.C. 103 as being unpatentable over Laseter et al and Freed et al as applied to claims 1-12 above, and further in view of Mudd et al and Frenkel et al.

Mudd et al show that elevated blood and urine levels of homocysteine and methylmalonic acid are associated with a deficiency in coenzymatically active vitamin B_{12} derivatives, even when total vitamin B_{12} levels are normal. Frenkel et al teach that elevated levels of methylmalonic acid are associated with cobalamin deficiency and that methylmalonic aciduria can reveal those instances where a cobalamin deficiency exists, but serum cobalamin levels are normal. It would have been obvious for one of ordinary skill in the art to determine cobalamin "or" folate deficiency indirectly by measuring homocysteine and methylmalonate levels, since it is known that direct methods may yield misleading results. With reference to claims 29-32, it is conventional in the art to relieve the symptoms of cobalamin or folate deficiency, regardless of the method of diagnosis, by administering cobalamin or folate.

Any inquiry concerning this communication should be directed to T. Sheiner at telephone number 703-557-8175.

/s/ TRS

SCHEINER : ew

7-14-88

retyped 7-15-88

/s/ Robert J. Warden
Robert J. Warden
Supervisory Patent Examiner
Art Unit 182

Defendant's Exhibit M

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

In re Application of:
Robert H. Allen
Sally P. Stabler
John Lindenbaum

Serial No. 933,553 Group Art Unit: 182

Filed: 20 November 1986 Examiner: T. Scheiner

For: Assay for Sulfhydryl Amino Acids and Methods for Detecting and Distinguishing Cobalamin and Folic Acid Deficiency

February 1989

Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

REQUEST FOR EXTENSION OF TIME

Applicants respectfully request that the period for responding to the Official Action of 1 August 1988 be extended for three (3) months so as to expire on 1 February 1989.

The Commissioner is hereby authorized to charge the necessary fees due under 37 CFR 1.17(c) to Deposit Account No. 21-0691. A duplicate copy of this sheet is enclosed.

AMENDMENT

* * * *

Rejection under 35 U.S.C. 112:

* * * *

Claim 13 should recite discrete, sequential process steps, for example, obtaining a sample, contacting the sample, etc. The final step should be clearly related to the preamble of the claim.

As Applicants are the first to detect cobalamin or folate deficiency by assaying body fluids for total homocysteine, it is believed that they are entitled to a claim of equivalent scope, not limited to any particular process steps or methods.

Claims 13-22 are vague and indefinite in their recitations of "elevated levels" and "normal levels" of total homocysteine The claims should include quantitative language.

As shown on page 18, first full paragraph, the normal range for homocysteine in human serum at the time this invention was made was understood to be 7-22 μmol/liter and in human urine was 1-20 μmol/liter. Higher (elevated) levels of homocysteine are indicative of cobalamin and/or folate deficiency. Methods for determining such ranges for different body tissues are well-known in the art. The claims are fully supported by the specification and Applicants see no reason why the claims should be limited to particular ranges.

* * * *

Rejection of Claims 13-21 under 35 USC 103:

Claims 13-32 are rejected under 35 U.S.C. 103 as being unpatentable over Laseter et al and Freed et al as applied to claims 1-12 above, and further in view of Mudd et al and Frenkel et al.

Mudd et al show that elevated blood and urine levels of homocysteine and methylmalonic acid are associated with a deficiency in coenzymatically active vitamin B12 derivatives, even when total vitamin B12 levels are normal.

Frenkel et al teach that elevated levels of methylmalonic acid are associated with cobalamin deficiency and that methylmalonic aciduria can reveal those instances where a cobalamin deficiency exists, but serum cobalamin levels are normal. It would have been obvious for one of ordinary skill in the art to determine cobalamin "or" folate deficiency indirectly by measuring homocysteine and methylmalonate levels, since it is known that direct methods may yield misleading results. With reference to claims 29-32, it is conventional in the art to relieve the symptoms of cobalamin or folate deficiency, regardless of the method of diagnosis, by administering cobalamin or folate.

Claim 13 concerns a method for detecting a deficiency of cobalamin or folate in warm-blooded animals by assaying body fluids for the presence of elevated levels of total homocysteine.

Claim 14 is similar to Claim 13 but it is specified that said assay is performed according to the method of Claim 7.

Claim 15 depends from Claim 13 and specifies that said assay comprises subjecting the sample to chromatography.

Claim 16 depends from Claim 15 and specifies that said chromatography is high performance liquid chromatography with an electrochemical detector set to respond to thiol groups.

Claim 17 depends from Claim 13 and specifies that the assay for the presence of elevated levels of total homocysteine comprises converting homocysteine present in the sample to labelled S-adenosylhomocysteine by exposure to S-adenosylhomocysteine hydrolase and radioactive S-adenosine, and quantifying the labelled S-adenosylhomocysteine.

Claim 18 concerns a method for detecting a deficiency of cobalamin, folate, or both in warm-blooded animals and distinguishing therebetween, comprising assaying body fluids for the presence of elevated levels of total homocysteine and methylmalonic acid, wherein normal levels of total homocysteine indicate no cobalamin or folic acid deficiency,

elevated levels of both total homocysteine and methylmalonic acid indicate cobalamin deficiency, and elevated levels of total homocysteine combined with normal levels of methylmalonic acid indicate folic acid deficiency.

Claim 19 is similar to Claim 18 except that said assay for total homocysteine is specifically performed according to the method of Claim 7.

Claim 20 depends from Claim 18 and specifies that said assay for total homocysteine is done via chromatography.

Claim 21 depends from Claim 20 and specifies that said chromatography is high performance liquid chromatography with an electro-chemical detector set to respond to thiol groups.

Claim 22 depends from Claim 18 and specifies that said assay for total homocysteine is done by converting any homocysteine present in the sample to labelled S-adenosylhomocysteine by exposure to S-adenosylhomocysteine hydrolase and radioactively labelled adenosine.

Claim 23 depends from Claim 18 and as amended specifies that the methylmalonic acid is assayed by: a) combining the tissue sample with an internal reference standard comprising a known amount of methylmalonic acid labelled with a stable isotope marker; b) measuring the relative amounts of labelled and unlabelled methylmalonic acid present with a mass spectrometer; c) calculating the ratio of labelled to unlabelled methylmalonic acid present; and d) deriving the amount of unlabelled methylmalonic acid present in the sample. The claim has been amended to clarify that relative amounts are measured in step (b), which are then quantified in step (d).

Claim 24 depends from Claim 23 and adds the step of derivatizing the labelled and unlabelled methylmalonic acid after addition of the internal standard and before measurement on the mass spectrometer.

Claim 25 depends from Claim 24 and specifies that the derivatives are silyl derivatives.

Claim 26 depends from Claim 25 and specifies that the silyl derivatives are obtained by exposing the methylmalonic acid to N-methyl-N-(t-butyldimethylsilyl) trifluoroacetamide.

Claim 27 depends from Claim 23 or 24 and specifies that the internal reference standard comprises deuterated methylmalonic acid.

Claim 28 depends from Claim 26 and adds the step of partially purifying the methylmalonic acid after step (a) and before step (b).

Claim 29 as amended concerns a method of treating humans for cobalamin deficiency, wherein at least one body tissue from said human is assayed for the presence of cobalamin deficiency according to the method of Claim 18, and thereafter sufficient cobalamin is administered to said human to return the total homocysteine levels to normal.

Claim 30 is similar to Claim 29 except that the cobalamin deficiency is assayed for by the method of Claim 18.

Claim 31 as amended concerns a method of treating humans for folic acid deficiency which comprises assaying for the presence of folic acid deficiency according to the method of Claim 13, and administering to the human enough folic acid to return the total homocysteine levels to normal.

Claim 32 is similar to Claim 31 except that the folic acid levels are assayed via the method of Claim 18.

The heart of these claims is the concept that total homocysteine is elevated in patients with cobalamin and folic acid deficiency, while methylmalonic acid values are elevated only in patients with cobalamin deficiency. The correlative values can be charted as follows:

	Total Homocysteine	Methylmalonic acid
Cobalamin deficiency	+	+
Folic acid deficiency	+	Normal

wherein "+" indicates an elevated level. It was not previously known that elevated levels of homocysteine correlate with cobalamin and folate deficiency, nor was it previously known or suggested to use a combination of assays for total homocysteine and methylmalonic acid to diagnose and distinguish between these deficiencies.

* * * *

Mudd, S.H., H.L. Levy, and R.H. Abeles, Chem. Abstr. (1969) 70:150 (Abstr. No. 113151p) [hereinafter Mudd] discloses high blood and urine levels of homocysteine and cystathionine and a decrease in methionine in a fatally ill infant, attributed to an inability to accumulate coenzymatically active vitamin B12. Total vitamin B12 levels were normal, suggesting that the defect was in metabolism rather than transport.

The Examiner is suggesting that because homocysteine was elevated in an infant with an inborn error in B12 metabolism, it would be obvious to assay everyone who is cobalamin deficient for elevated levels of homocysteine. This logic is erroneous. Since B12 levels were normal, it is clear that this infant was not suffering from B12 deficiency. There is no teaching that high levels of total homocysteine in such genetically impaired infants correlates with cobalamin deficiency in normal humans.

Dr. Mudd himself, in a book published in 1974 (five years after the above-cited work) stated:

> . . . Insufficient data are available to establish whether homocystinuria is a rare or common manifestation in untreated patients with selective genetic malabsorption of B12. If it is common, the question arises as to whether patients with B12 deficiency for other reasons are homocystinuric. Patients with untreated pernicious anemia [the most common cause of cobalamin deficiency] in some cases have mild non-specific aminoaciduria but homocystinuria has not been mentioned. . . . B12-

> deficient pigs have . . . an abnormal elevation of serum homocysteine-cysteine mixed disulfide. It would be worthwhile to reexamine with modern sensitive methods the plasma of B12-deficient patients for such changes, and their urine for possible homocystinuria. Such studies would also be of interest in patients with malabsorption of vitamin B12 due to genetically determined absence of intrinsic factor activity or with genetic malabsorption of foic acid. [citations omitted, comment added]

Mudd, S.H. in Heritable Disorders of Amino Acid Metabolism: Patterns of Clinical Expression and Genetic Variation, W.L. Nyhan, ed. (John Wiley & Sons, New York, 1974), pp.436-437 [copy enclosed for the convenience of the Examiner].

Thus, even five years after the referenced work, Mudd is not sure whether homocystinuria is commonly associated with genetic malabsorption of B12 or is ever seen in other causes of cobalamin deficieny, including the most common, pernicious anemia. While Mudd suggests it would be interesting to examine the urine for elevated levels of homocysteine, he is by no means teaching that such a correlation exists. It was not until the work of the present inventors that the correlation was tested and proven.

* * * *

Defendant's Exhibit P

[SEAL]

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

06/933,553	11/20/86	ALLEN	R	CU280/281

BARBARA A. SHIMEI
UNIVERSITY PATENTS, INC.
P.O. BOX 901
WESTPORT, CT 06881

EXAMINER	
SCHEINER, T	
ART UNIT	PAPER NUMBER
182	4

DATE MAILED:

05/26/89

* * * *

Part II SUMMARY OF ACTION

1. ☒ Claims 1-32 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☒ Claims 1-12, 14 and 18-28 are free of the prior art of record.

4. ☒ Claims 13, 15-17 and 29-32 are rejected.

* * * *

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless-

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 13 and 15-17 are rejected under 35 U.S.C. 102a or b as being anticipated by Applicants' admitted state of the prior art.

In the absence of a correlation step, the preamble of claim 13 merely recites an intended use of the invention. The claim lacks a positive limitation for correlating to a particular condition and has only one method step recited. Applicants admit on pages 12 and 13 of the specification that assays for homocysteine are known. With respect to claims 15-17, applicants further admit that measurement of homocysteine by HPLC is conventional (R. Saetre et al, 1978), as is measurement of homocystein converted to S-adenosylhomocysteine (H. Refsum et al, 1985).

The text of those sections of Title 35 U. S. Code not included in this action can be found in a prior Office action.

Claims 29-32 are rejected under 35 U.S.C. 103 as being unpatentable over Applicants admitted state of the prior art.

On page 3 of the specification, and numerous other locations, applicants admit that treatment of diagnosed cobalamin or folic acid deficiencies by administration of cobalamin or folic acid, respectively, is conventional in the art. It would have been obvious for one of ordinary skill in the art to relieve the symptoms of cobalamin or folate deficiency, regardless of the method of diagnosis, by administering cobalamin or folic acid. In corporation of the instant method of diagnosis into an old treatment protocol does not provide unexpected results and cannot be considered unobvious (In re Durden, Jr. et al 226 USPQ 359).

R. Saetre et al and H. Refsum et al, cited on page 12 of the specification are unavailable to the examiner. It is requested that Applicant supply these pertinent references in order to comply with 37 CFR 1.56.

Claims 1-12. 14 and 18 are free of the prior art of record.

The references kindly supplied by Applicants in their Information Disclosure Statement of April 20, 1989 have been considered, however, a listing of the references on PTO form 1449 to complete the record would be greatly appreciated.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Toni R. Scheiner whose telephone number is (703) 557-8175.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 557-0664.

Scheiner-fg

5/24/89

/s/ TRS

/s/ Robert J. Warden
Robert J. Warden
Supervisory Patent Examiner
Art Unit 182

Defendant's Exhibit R

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	I hereby certify that this paper is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope addressed to: Commissioner of Patent and Trademarks, Washington, D.C. 20231, on this date:
Allen et al.	
Serial No: 06/933,553	
Filed: 20 November 1986	
For: ASSAY FOR SULFHYDRYL AMINO ACIDS AND METHODS FOR DETECTING AND DISTINGUISHING COBALAMIN AND FOLIC ACID DEFICIENCY	September 14, 1989 (Date)
Group Art Unit: 182	/s/ Lewis S. Gruber Lewis S. Gruber (30,060) Attorney for Applicant(s)
Examiner: T. SCHEINER	

AMENDMENT UNDER 37 C.F.R. §1.115

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sirs:

In an Office Action mailed May 26, 1989 (the period for response to which is extended to September 26, 1989 by a Petition for Extension of Time enclosed herewith) claims 13 and 15-17 were rejected under 35 U.S.C. §102(a) or (b) and claims 29-32 were rejected under 35 U.S.C. §103. Claims 1-12, 14 and 18-28 were indicated to be free of the prior art of

record. In response, reconsideration is respectfully requested in light of the following amendments and remarks.

In the Claims

Please amend claim 13 and please add claims 33 and 34 as follows.

13. (Amended) A method for detecting a deficiency of cobalamin or folate in warm-blooded animals [by] comprising the steps of:

assaying a body fluid[s] for [the presence of] an elevated level[s] of total homocysteine[.]; and

correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

33. The method for detecting a deficiency of cobalamin or folate, as recited in claim 13, wherein said assaying *comprises the* step of determining an elevated level of total homocysteine in a human body fluid.

34. The method for detecting a deficiency of cobalamin, folate, or both, as recited in claim 18, wherein said assaying step comprises the step of determining elevated levels of total homocysteine and methylmalonic acid in a human body fluid.

REMARKS

Claims 1-32 are pending to the present application. In the above-cited Office Action, claims 1-12, 14 and 18 were noted by the Examiner to be tree of the prior art of record.

Saetre et al., Anal. Biochem., 90, 684-697 (1978) and Refsum et al., Clin. Chem., 31(4) 624-628 (1985), cited on page 12 of the Specification, were indicated to be unavailable to the Examiner. It was requested that the Applicants supply these references.

In response, copies of Saetre et al. and Refsum et al. are enclosed.

The Examiner noted that references supplied by Applicants in their Information Disclosure Statement of April 20, 1989 had been considered, however, a listing of the references on PTO-Form .1449 to complete the record would be greatly appreciated.

In response, a PTO-Form 1449 listing the previously-cited references is enclosed.

It should be noted that the designations of Mudd et al., Refsum et al. and Saetre et al as Documents 4, 7 and 9 in the enclosed PTO-Form 1449 are those of the previously submitted Information Disclosure Statement and not those in the PTO-Form 892 b[e] mailed by the Examiner with the Official Action on May 26, 1989.

A Supplemental Information Disclosure Statement and PTO-Form 1449 addressing additional art are also enclosed.

Since the filing of the last response, it was noted that the group of claims related to claim 13 and the group of claims related to claim 18 had no member specifically reciting a step for use with a human subject. Inasmuch as the Examples are directed to and support practice of the present invention with human subjects, it was believed to be appropriate to amend the application to add claims specifically directed to human uses.

Because new claims 33 and 34 properly depend from claim 13 and claim 18, respectively, and because each is a proper species of the genus of the claim from which it depends, it is submitted that no new search is required, and that claims 33 and 34 should be entered as proposed. All claims of the present application are believed to be in condition for allowance.

A. The Rejections under 35 U.S.C. §102 (a) or (b) May Properly Be [W]ithdrawn

In the above-cited Office Action claims 13 and 15-17 were rejected under 35 U.S.C. §102(a) or (b) as being anticipated by Applicants' admitted state of the art.

In the absence of a correlation step, the preamble of claim 13 was asserted by the Examiner to merely recite an intended use of the invention in that the claim lacked a positive limitation for correlating to a particular condition and had only one method step recited. The Examiner further asserted that Applicants admitted on pages 12 and 13 of the specification that assays for homocysteine were known, and that, with respect to claims 15-17, Applicants admitted that measurement of homocysteine by HPLC was conventional [citing Saetre et al., Anal. Biochem., 90, 684-697 (1978)], as was measurement of homocysteine converted to S-adenosylhomocysteine [citing Refsum et al., Clin. Chem., 31(4) 624-628 (1985)].

In response claim 13, and hence claims 15-17 by dependency therefrom, has been amended to recite a second step of correlating an elevated level of total homocysteine with a deficiency of cobalamin or folate.

This amendment was made without any intention to abandon any subject matter within the scope of the claims as originally filed and it is intended that claims of .the scope of the claims as originally tiled may be pursued in continuation or continuation-in-part applications.

Claims 13 and 15-17 go beyond the mere recitation of an intended use to provide a two step method which includes a correlating step not found in Refsum et al., or Saetre et al. Specifically, neither Refsum et al. nor Saetre et al. correlate levels of homocysteine in a body fluid with cobalamin or folate deficiency.

Inasmuch as a proper reference under 35 U.S.C. §102(a) or (b) must disclose all elements of a claim and inasmuch as Refsum et al. and Saetre et al. do not recite the step correlating homocysteine levels to a cobalamin or folate deficiency, Refsum et al. and Saetre et al. are not proper references against claims 13 and 15-17 under 35 U.S.C. §102(a) or (b) and the rejection under this section should be withdrawn.

B. The Rejection under 35 U.S.C. §103 May Properly Be Withdrawn

In the above-cited Office Action claims 29-32 were rejected under 35 U.S.C. §103 as being unpatentable over Applicants' admitted state of the art upon the Examiner's assertion that, on page 3 of the Specification, and at numerous other locations, Applicants admitted that treatment of diagnosed cobalamin or folic acid deficiencies by administration of cobalamin or folic acid, respectively, was conventional in the art. The Examiner further asserted that it would have been obvious for one of ordinary skill in the art to relieve the symptoms of cobalamin or folate deficiency, regardless of the method of diagnosis, by administering cobalamin or folic acid. Incorporation of the instant method of diagnosis into an old treatment protocol was asserted not to provide unexpected results so that this could not be considered unobvious [citing In re Durden, 226 USPQ 395].

In response, it is respectfully submitted that In re Durden relates to the use of a new starting material in an otherwise old process or to the production of a new product in a process which is otherwise old. See In re Durden, 226 USPQ 359, 362 (Fed. Cir. 1985). In claims 29-32 of the present application, a new combination of process steps its provided, a situation to which In re Durden is not directed.

Moreover, the Examiner's comment that it is obvious to relieve symptoms of cobalamin or folate deficiency by administering cobalamin or folate is the basis for an improper rejection of a method claim on the basis that some of its steps are old. In fact, the court in In re Durden did address the issue of whether a claim must be considered as a whole, and indicated that it did.

The Applicant has not admitted, and the Examiner has not asserted, that there was in the prior art a suggestion to combine the steps recited in claims 29-32. Absent a proper suggestion in cited art to combine the steps, the combination of steps of claims 29-32 is not properly rejected as obvious.

Furthermore, the diagnostic steps of processes which are admitted by the Examiner to be free of the art of record (i.e.,

the steps of claim 18 referenced in claims 30 and 32) or which are established in Section A of this Amendment to be free of art (i.e., the steps of claim 13 referenced in claims 29 and 31) are novel and nonobvious and render novel and nonobvious all claims in which they are recited in combination with other elements. In this regard, it is respectfully submitted that it is improper to reject claims 29-32 as obvious over art in combination with the Applicants' invention of claims 13 and 18.

Therefore, because the method claimed in claims 29-32 is new and nonobvious, unlike the process of In re Durden which process was old but was sought to be patented on the basis of its application to a new starting material, the rejection under 35 U.S.C. §103 should be withdrawn.

Summary

In light of the foregoing amendments and remarks, it is believed that the rejections for obviousness and under 35 U.S.C. §102(a) or (b) and under 35 U.S.C. §103 have been overcome and that claims 13, 15-17 and 29-32, along with all other claims in the present application, are now in condition for allowance.

Respectfully submitted,

MARSHALL, O'TOOLE,
GERSTEIN,MURRAY
& BICKNELL

BY: /s/ Lewis S. Gruber

Lewis S. Gruber (Reg. No. 30,060)
Two First National Plaza Suite 2100
Chicago, IL 60603
(312) 346-5750

Defendant's Exhibit T

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	)	I hereby certify that this
	)	paper is being deposited
Robert H. Allen et al.	)	with the United States
	)	Postal Service as first
Serial No: 06/933,553	)	class mail, postage prepaid,
	)	in an envelope addressed to:
Filed: 20 November 1986	)	Commissioner of Patents and
	)	Trademarks, Washington, D.C.
For: Assay for Sulfhydryl	)	20231, on this date:
Amino Acids and Methods for	)	
Detecting and Distinguishing	)	September 14, 1989
Cobalamin and Folic Acid	)	(Date)
Deficiency	)	
	)	/s/ Lewis S. Gruber
Group Art Unit: 182	)	Lewis S. Gruber (30,060)
	)	Attorney for Applicant(s)
Examiner: T. Scheiner	)	

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §1.97 INCLUDING FORM PTO-1449

TO: Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

Sirs:

In compliance with Title 37 of the Code of Federal Regulations, Sections 1.97, et seq., enclosed is a Form PTO-1449 listing documents disclosed to the Examiner by this Information Disclosure Statement.

The significance of each document cited on the Form PTO-1449 is discussed below. However, if further comment on any reference would be of assistance to the Examiner, advice of same is solicited. In addition, the Examiner is urged to

undertake an independent review of the documents to assure that all aspects of the documents relevant to the present invention are considered.

Document C18, Stabler et al., Blood, 66 (Suppl.), Abstract 87, 50a (Am. Soc. Hem. Meeting) (1985) is a publication coauthored by the Applicants and published less than one year prior to the filing date of the present application. Document C18 relates to an assay for serum homocysteine which is stated to be converted to methionine by the cobalamin-dependent enzyme methionine synthetase which also converts homocysteine and methyltetrahydrofolate. Also in Document C18, it is stated that infusion of a cobalamin analogue, OH-cobalamin(c-lactam], reduced mean rat liver methionine synthetase activity and increased mean serum homocysteine. Exposure to 50% nitrous oxide for 36 hours is reported to have reduced mean synthetase and increased mean serum homocysteine. Injections of OH-cobalamin are reported to have elevated mean synthetase and decreased mean serum homocysteine.

In Document C18, it is concluded that: 1) homocysteine can be detected and quantitated in normal serum, 2) serum homocysteine is elevated in almost all untreated patients with cobalamin or folate deficiency and will be useful diagnostically, and 3) serum homocysteine is a sensitive indicator of methionine synthetase activity in humans and rats.

In a telephone conference with Michael de Nardo, a person represented by the publisher of Blood as having records of distribution data for issues of this journal in November 1985, Mr. de Nardo reported that the mailing date for the Volume 66 Abstract issue (November 1985) of Blood was November 24, 1985. As a publication less then one year prior to the date of the present application and deriving its disclosure from the Applicants, Document C18 is not a proper reference against the present application.

Moreover, Document C18 does not disclose the combination of assays for MMa and homocysteine which may be used to distinguish cobalamin and folate deficiencies and to treat such deficiencies according to the present invention.

Document C3, Brattstrom et al., Metabolism, 34(11), 1073-1077 (1985), relates to homocysteinemia and the observation that administration of folic acid to individuals whose folates and cobalamins are above or within normal ranges reduces homocysteine. Document C3 is concerned with reducing circulating homocysteine concentration in nonfolate-deficient men and women (see page 1076).

No suggestion is made that folate or cobalamin deficiency is related to homocysteinemia. In this regard excess folate is described, at page 1076, as a mass action effector to cause conversion of excessive homocysteine to methionine not as therapy for a deficiency.

Although it is noted that deficiencies of certain enzymes in pathways involving homocysteine or methionine result in homocysteinemia, Document C3 does not disclose the particular problems of assaying for sulfhydryl amino acids disclosed in the present application, nor does Document C3 suggest the solution to the problems according to the present invention as recited in claim 1, specifically, mixing a labeled reference standard with a sample, adding sufficient reducing agent to randomize the labeled and unlabeled sulfhydryl amino acids, and measuring the amount of labeled and unlabeled sulfhydryl amino acid present. Moreover, Document C3 does not disclose any advantage of an assay for MMa or of an assay for a sulfhydryl amino acid, such as homocysteine, or both with respect to the diagnosis or treatment of cobalamin or folate deficiency.

Thus, although Document C3 relates to treatment of homocysteinemia with folic acid, it does not disclose or suggest proper combination with other documents of record to disclose the method of assaying for a sulfhydryl amino acid or the use of assays for MMa or homocysteine or both for diagnosis and treatment of cobalamin or folate as claimed in the present application.

* * * *

Defendant's Exhibit Z

University Science, Engineering and Technology, Inc.
1465 Post Road East
P.O. Box 915
Westport, CT 06881-0915
(203) 259-7997

October 26, 1990

CONFIDENTIAL

Dr. Robert H. Allen
President
Metabolite Laboratories, Inc.
4001 S. Dexter Street
Inglewood, Colorado 80110

Re: CU 280/281 - Assay for Sulfhydryl Amino Acids and Methods for Detecting and Distinguishing Cobalamin and Folic Acid Deficiency
License Agreement: UPI and Metabolite Laboratories, Inc.
Dated as of 22 November, 1988 (the "License Agreement")

Dear Dr. Allen:

You have advised me that Metabolite Laboratories, Inc. ("Metabolite") desires to enter into a relationship with Roche Diagnostics (and perhaps other entities as well) under which Metabolite will sublicense the rights granted to it by UPI in the License Agreement. Further, you have advised me that the ability of Metabolite to sublicense may enhance the rate of commercial exploitation of the invention. In consideration of the foregoing, University Patents, Inc., as licensor under

the License Agreement, agrees to amend, and does hereby amend the License Agreement, as follows:

1. Section 2.02 of the License Agreement is deleted in its entirety, and in substitution thereof, is inserted:

"Section 2.02 During the term of this Agreement, the license hereby granted shall include the right of LICENSEE to grant written sublicenses, provided that LICENSEE shall include all Sales made by all sublicensees in its reports to UPI as provided in Section 4.03 and pay royalties to UPI as though all such transactions by sublicensees were in fact made by LICENSEE hereunder. LICENSEE agrees to deliver to UPI a notice of each and every sublicense entered into by LICENSEE within thirty (30) days after execution thereof and shall promptly advise UPI in writing of any modification or termination of each sublicense. Each notice shall contain the name and address of each sublicensee, the title or designation of its responsible officer, the term and geographic limitations, if any, of the sublicense, and shall contain a representation that the sublicensee has been made aware of the essential terms of this Agreement, including (by way of example and not limitation) the following provisions: (1) royalty obligations; (2) accounting; (3) default; (4) warranty; (5) assignment; (6) indemnification and (7) restriction on the use of the name of the University of Colorado. Upon termination of this Agreement for any cause, any and all existing sublicenses hereunder shall thereupon be assigned to UPI. This shall be made a condition of any such sublicense that may be granted by LICENSEE."

2. In all other respects, the License Agreement is hereby affirmed and ratified and remains in full force and effect.

Sincerely,

University Patents, Inc.

By: /s/ [Illegible]
Vice President

ACCEPTED AND AGREED TO
This 2nd day of November, 1990

Metabolite Laboratories, Inc.

By: /s/ Robert H. Allen
President

RIS/mbe

cc: J. Holloway
H. Jacobson
J. Lindenbaum

Defendant's Exhibit AB

University of Colorado Health Sciences Center
Department of Medicine
Division of Hematology
Campus Box B170 School of Medicine
4200 East Ninth Avenue
Denver, Colorado 80262
(303) 270-8474

June 4, 1992

Dr. Peter W. Wentz
Director of Toxicology
Roche Biomedical Laboratories
1447 York Court
Burlington, NC 27296

Dear Peter,

As we discussed on the telephone yesterday, I am very pleased that things are running smoothly with you in terms of the performance of the metabolite assays. I will always be glad to answer any technical questions that arise concerning the metabolite assays and Dr. Sally P. Stabler and myself will be glad to answer any questions that physicians might have regarding the results or interpretations of the metabolite assays.

One aspect of the metabolite assays that I did not mention in our conversations concerns the occasional request that only one of the metabolites be performed rather than all four. I have always refused to do this because I do not believe that it is good medical practice. My reasoning is based on the fact that a normal value for one metabolite does not exclude the possibility that one or more of the additional metabolites may be elevated as well as the fact that an isolated elevated value for one metabolite can not be interpreted completely without knowing whether the other metabolites are also

elevated or are normal. There are also technical and possible economic reasons for not separating the metabolite assays but these are overshadowed by the importance of good medical practice as just noted above. If you have any questions about this aspect of the metabolites or if this becomes an issue in the future, I hope you will feel free to ask me for any assistance that I might provide in this matter.

I am also enclosing four tables that might serve as a starting point for a brochure or physician education piece about the indications, utility and interpretation of the metabolite assays. You may want to alter the normal ranges that I have listed for serum vitamin B_{12} and folate to match those of Roche Biomedical Laboratories and I hope that you and your marketing people will feel free to make any other changes that you believe would be helpful. I am also enclosing reprints of several articles that you may wish to list as a bibliography at the end of an education piece regarding the metabolite assays.

Please let me know if I can be of any further assistance.

With best regards,

Sincerely yours,

/s/ Bob
Robert H. Allen, M.D.
Professor of Medicine
Professor of Biochemistry
Director, Division of Hematology

RHA:vla

Enclosures

Defendant's Exhibit AC

AGREEMENT

This Agreement effective as of the 31st day of January, 1991 ("Effective Date") by and between Hoffmann-La Roche Inc., a New Jersey corporation having offices at 340 Kingsland Street, Nutley, New Jersey 07110 (hereafter "HLR") and Metabolite Laboratories, Inc., a Colorado corporation, having offices at No. 4001 S. Dexter Street, Englewood, Colorado 80110 (hereafter "MLI");

WITNESSETH

WHEREAS, MLI represents and warrants that it has the full power and authority to grant sublicenses under the invention disclosed and claimed in Un[it]ed States Patent 4,940,658, issued July 10, 1990, entitled "Assay for Sulfhydryl Amino Acids and Methods for Detecting and Distinguishing Cobalamin and Folic Acid Deficiency", inventors Robert H. Allen, Sally B. Stabler and John Lindenbaum including any patents issuing from any continuations, continuations-in-part, divisions and/or reissues thereof (hereafter "Licensed Patents") as evidenced in part by a License Agreement between University Patents, Inc. (hereafter "UPI") and MLI dated November 22, 1988, and a letter amendment thereof dated October 26, 1990 granting MLI the right to sublicense (hereafter collectively referred to as "Prior Agreement"), a copy of which are attached to this Agreement and have been reviewed by HLR;

WHEREAS HLR is a major healthcare company which, through its Roche Biomedical Laboratories (hereafter "RBL") subsidiary, provides commercial clinical laboratory services to the medical community and is desirous to obtain rights to commercially offer (i) assays of homocysteine using methods and materials falling within the claims of the Licensed Patents; (ii) assays of methylmalonic acid utilizing

mass spectrometry or using methods and materials falling within the claims of the Licensed Patents; (iii) assays of 2-methylcitric acid utilizing mass spectrometry or used to detect Vitamin B_{12} or Folic Acid deficiencies; and (iv) assays of cystathionine utilizing mass spectrometry or used to detect Vitamin B_{12} or Folic Acid deficiencies (hereafter collectively referred to as the "Licensed Assays");

WHEREAS MLI is agreeable to extend a sublicense under Licensed Patent to HLR and to grant HLR certain rights to commercially utilize future improvements, whether or not patentable, to Licensed Assays and to proprietary technology relating to automated apparatus for carrying out Licensed Assays which may be developed by MLI during the term of this Agreement (hereafter collectively "Licensed Rights") in return for HLR's commitment to be bound by all relevant terms and conditions of Prior Agreements and its agreement to the undertakings set forth in this Agreement;

NOW, THEREFORE, in consideration of these premises and of the mutual covenants hereinafter set forth, HLR and MLI mutually covenant and agree as follows:

ARTICLE I - GRANTS

1.01 Subject to the terms and conditions of this Agreement, MLI agrees to grant and hereby grants to HLR a nonexclusive license to the Licensed Rights and a nonexclusive sublicense under the Prior Agreements to the Licensed Patents which license and sublicense shall be for the practice of Licensed Assays in the United States.

1.02 MLI agrees that promptly after the Effective Date it will provide to RBL, at a place and in a manner reasonably designated by RBL, calibrators used in performance of the Licensed Assays and all technology and know-how including technology relating to automated apparatus reasonably needed by RBL to carry out commercial operations with Licensed Assays at no additional cost to RBL. RBL will be free

to apply the technology and know-how relating to the automation of the assay to any related or unrelated assay not covered by this Agreement without additional consideration.

1.03 MLI agrees to provide RBL, at RBL's request, with the right to refer samples to MLI and MLI will conduct Licensed Assays on such samples (hereafter "Referral Assays") and provide RBL with the results of such test in accordance with normal business practice.

ARTICLE II - PAYMENTS UNDER THE LICENSES

2.01 In consideration of the grants made in ARTICLE I, HLR agrees to pay to MLI a royalty of 43% in respect to HLR's Net Sales (as defined below) of Referral Assays.

2.02 In consideration of the grants made in ARTICLE 1, HLR agrees to pay to MLI a royalty of 21.5% in respect to HLR's Net Sales of Licensed Assays other than Referral Assays.

2.03 Additionally, HLR agrees to pay to UPI or an affiliated company designated by UPI, all royalties due to UPI under the terms and conditions of Prior Agreement on Sales (as defined in Prior Agreement) of Referral Assays and Licensed Assays.

2.04 The term "Net Sales" as used herein shall mean the sales price of Licensed Assays or Referral Assays actually received by HLR or its Affiliates (as defined herein) upon sales to first customers of such Assays after deducting returns, sales rebates, cash discounts, sales taxes or other taxes directly linked to the sale of such Assays. Sales of such Assays between or among HLR and its Affiliates shall not be considered in the computation of Net Sales, but sales by Affiliates of HLR to customers of HLR or its Affiliates

shall be included. For purposes of this Section 2.04, the term "Affiliate" shall mean:

i) a business entity which owns, directly or indirectly, a controlling interest in either party, by stock ownership or otherwise; or,

ii) a business entity which is owned by either party, either directly or indirectly, by stock ownership or otherwise; or,

iii) a business entity, the majority ownership of which is directly or indirectly common to the majority ownership of either party;

iv) Affiliate shall not mean Genentech, Inc.

ARTICLE III - ACCOUNTING

3.01 Royalty payments due hereunder in connection with Net Sales of Licensed Assays other than Referral Assays shall be computed on a quarterly accounting period ending on the last day of each calendar quarter for each License Year (as defined in Prior Agreement) during the term of this Agreement. Payments hereunder shall be made within sixty (60) days following each quarterly period, and each payment shall include the royalties during the most recent quarterly accounting period. Royalty payments in connection with Net Sales of Referral Assays will be invoiced by MLI on a monthly basis with payment due within thirty (30) days of receipt of invoice by HLR. Payments to UPI pursuant to Section 2.03 shall be made in the manner and at the times set forth in Article IV of the Prior Agreements.

3.02 Payments made hereunder shall be made in United States Dollars.

3.03 All royalty payments made in accordance with 3.01 shall be accompanied by a report certified by an officer of HLR setting forth the quantity of Licensed As-

says conducted by or on behalf of HLR and its Affiliates and documentation of the basis for calculating the Net Sales and Sales made by HLR and its Affiliates to include copies of any reports wherefrom Net Sales and Sales can be determined and the calculation of the royalties payable can be made. Such reports shall also be made if no royalties are due. For a period of two (2) years after each royalty period, HLR shall keep records pertaining to such royalty period in sufficient detail to permit the determination of royalties payable hereunder and at the request and expense of MLI will permit an independent Certified Public Accountant, selected by MLI and acceptable to HLR, or any other person acceptable to both MLI and HLR, to examine during ordinary business hours once in each calendar year such records as may be necessary to verify or determine royalties paid or payable under this Agreement. Such Certified Public Accountant or other person shall report to MLI only the amount of royalties due and payable.

3.04 Upon termination or expiration of this Agreement, HLR shall pay to MLI and UPI within sixty (60) [d]ays after such termination or expiration, all unpaid royalties accrued until such time.

ARTICLE IV - TERMINATION

4.01 The term of this Agreement shall be from the Effective Date until the date of expiration of the last to expire of the Licensed Patents.

4.02 HLR shall have the right at any time on sixty (60) days prior written notice to MLI to terminate this Agreement with respect to a particular Licensed Assay if (i) in the case of Licensed Assays of homocysteine, a more cost effective commercial alternative is available that does not infringe a valid and enforceable claim of the Licensed Patents; (ii) in the case of Licensed Assays of methylmalonic acid, a more cost

effective commercial alternative is available that does not utilize mass spectrometry and does not infringe a valid and enforceable claim of the Licensed Patents; (iii) in the case of Licensed Assays of 2-methylcitric acid, a more cost effective commercial alternative is available that does not utilize mass spectrometry and is not used to detect Vitamin B_{12} or Folic Acid deficiencies; and (iv) in the case of Licensed Assays of cystathionine, a more cost effective commercial alternative is available that does not utilize mass spectrometry and is not used to detect Vitamin B_{12} or Folic Acid deficiencies. MLI shall have the right on sixty (60) days prior written notice to HLR to terminate this agreement if there has been no payment made to MLI during any eight (8) consecutive quarters if HLR permanently discontinues offering Licensed Assays and Referral Assays.

4.03 MLI shall have the right to terminate this Agreement on sixty (60) days prior written notice in the event (i) that HLR is in material breach of a provision of this Agreement and such breach is not cured during such notice period then MLI can terminate in thirty (30) days on providing a second written notice; or (ii) that HLR shall become bankrupt or insolvent, or if HLR's business shall be placed in the hands of a receiver, assignee or trustee whether by the voluntary act of HLR in the course of in[s]olvency proceedings. MLI shall have the right to discontinue conduct of Referral Assays during the continuance of any material breach of a provision of this Agreement by HLR if such breach shall be uncorrected twenty (20) days after the written notice of such breach.

4.04 Any termination under this ARTICLE IV shall not relieve HLR or MLI of any obligation or liability accrued hereunder prior to termination, or rescind or give rise to any right to rescind anything done or any payments made or other considerations given here-

under prior to the time such termination becomes effective; and such termination shall not affect in any manner any remedy of either party arising out of this Agreement prior to such termination.

4.05 Upon termination of the Prior Agreements between UPI and MLI for any reason, the sublicense under the Prior Agreements to the Licensed Patents granted to HLR hereunder shall continue in full force and effect and shall be deemed to be assigned by MLI to UPI. It is expressly understood that such assignment shall not operate to expose HLR to any further obligations than are set forth in this Agreement.

ARTICLE V - NOTICE

5.01 Any payment, notice or other communication required or permitted to be made or given to either party hereto pursuant to this Agreement shall be sufficiently made or given on the date of mailing if sent to such party by certified or registered mail, postage prepaid, addressed to it at its address set forth below, or to such other address as it shall designate by written notice given to the other party as follows:

In the case of MLI:

President
Metabolite Laboratories, Inc.
4001 S. Dexter Street
Englewood, Colorado 80110

In the Case of HLR:
Notices to be sent to:

Roche Biomedical Laboratories
430 Spring Street
Burlington, North Carolina 27215
Atten: Brad Smith, Esq. and Mr. Ernie Knesel

With copy to:

Corporate Secretary
Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110

5.02 MLI agrees that it will be responsible for all notices regarding the extension of a sublicense under Prior Agreement which may be required to be made to UPI and, except as provided in Section 2.03, shall take all steps needed to maintain the Prior Agreement in full force and effect during the term of this Agreement.

ARTICLE VI - MISCELLANEOUS PROVISIONS

6.01 MLI warrants and represents that it has the full right and power to enter into this Agreement, and that there are no outstanding agreements, assignments, or encumbrances inconsistent with the provisions of this Agreement other than as may be expressly set forth herein. MLI represents that it is aware as of the Effective Date of no facts that would render Licensed Patents invalid or unenforceable. MLI makes no other representation or warranty, express or implied, including warranty, guaranty or representation as to the safety and efficacy of the Licensed Assays, nor does MLI assume any liability in respect of any infringement of patents or other rights of third parties due to HLR's operation under the license and sublicense herein granted. MLI represents that it is not aware as of the Effective Date of any claim or assertion by any third party that the performance of Licensed Assays or Referral Assays would infringe patent rights or other rights of such third parties.

6.02 All services and other transactions between the parties with respect to commercial activities in support of Referral Assays and/or Licensed Assays shall be made in accordance with the respective party's then established customary business terms generally of-

fered to the trade. In the event of a conflict between such customary business terms and the express terms of this Agreement then the express terms of this Agreement shall control.

6.03 This Agreement and the license rights granted shall not be assignable by HLR without the prior written consent of MLI, which shall not be unreasonably withheld, except that HLR may assign this Agreement and the license rights herein granted in connection with the sale and transfer of substantially all of the business assets of RBL, or of HLR's consolidation or merger with another company; provided that such assignee shall assume, in writing, all of the obligations of HLR hereunder.

6.04 Each party agrees that nothing contained herein shall be construed as conferring any right to use in advertising, publicity or other promotional activities in the name, insignia, symbols or other designation of the other party to this Agreement or any other party of the Prior Agreement with respect to any promotional activity associated with this Agreement or assays licensed hereunder without the written consent of the other party.

6.05 This Agreement shall be construed and the legal relations between the parties determined, in accordance with the laws of the State of New Jersey.

6.06 If any provision of this Agreement shall be held to be invalid, illegal, or unenforceable, the validity, legality and enforceability of the remaining provisions shall not in any way be affected or impaired thereby.

6.07 The headings of the several sections are inserted for convenience of reference only and are not intended to be part of or to affect the meaning or interpretation of this Agreement.

6.08 This Agreement embodies the entire understandings of the parties and supercedes any other agreement or understandings between the parties relating to the subject matter hereof. No waiver, amendment or modification of this Agreement shall be valid or binding upon such parties unless made in writing and signed on behalf of each such party by its respective proper officers thereto duly authorized.

6.09 All obligations and benefits made or received by HLR hereunder may be performed or received by RBL without prior notice to MLI.

ARTICLE VII - MOST FAVORED LICENSEE

7.01 In the event that MLI shall grant any other party rights to Licensed Assays or Referral Assays at terms and conditions more favorable to such other party than are granted to HLR hereunder, then MLI agrees to give HLR prompt written notice of that fact and HLR shall have the right to receive such more favorable terms provided that HLR shall agree to be bound by all other relevant terms and conditions granted such other party.

ARTICLE VIII - CONFIDENTIALITY

8.01 For the purposes of this Agreement, "Confidential Information" shall mean any information, whether written or oral, that is furnished or disclosed by MLI, or its employees, representatives or agents, relating to the Prior Agreements or the Licensed Assays or to the business, financial condition, strategies, plans, policies, clients or customers, inventions, trade secrets, computer programs, or processes of MLI. For the purposes of this Agreement, "Recipients" shall mean HLR and its Affiliates and their respective directors, officers, partners, employees, agents or representatives, and any or all of them, to the extent such persons receive Confidential Information.

8.02 (a) HLR agrees not to use the Confidential Information received from MLI for any other purpose except the purposes of this Agreement;

(b) to treat the Confidential Information received from MLI as it would its own proprietary information and to provide the Confidential Information to Recipients solely on a need to know basis; and,

(c) to take all reasonable precautions to prevent the disclosure of the Confidential Information received from MLI hereunder to any third party, other than Affiliates, without the express written consent of MLI. Upon termination, at MLI's request, HLR agrees to return all copies of Confidential Information to MLI, except HLR may retain one copy in a limited access file for archival purposes only.

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be duly executed as of the date first written above.

HOFFMANN-LA ROCHE INC.

By: /s/ Illegible

Title: Vice President

Date: 2-14-91

METABOLITE LABORATORIES INC.

By: /s/ Robert H. Allen

Title: President

Date: 2/6/91

Defendant's Exhibit AH

COMPETITIVE TECHNOLOGIES
1960 Bronson Road
Fairfield, CT 06430
(203) 255-6044

Releases

American Heart Association Recommends Homocysteine Testing

Available Now, Simple Test Uncovers Potential Heart Problems - Likely to Become as Common as Cholesterol Testing

FAIRFIELD, CT. (January 5, 1999)—In the current issue of its weekly journal, "Circulation," an American Heart Association Science Advisory urges doctors to begin screening high-risk patents with a personal or family history of heart disease for elevated homocysteine levels.

The advisory comes in the wake of a number of recent studies, including a 14-year study at the Harvard School of Public Health involving 80,000 women, which concluded that high homocysteine levels play a central role in cardiovascular disease. An estimated 20 million Americans, more than one of every three people with heart disease, experience high levels of homocysteine. This means that screening for the problem could significantly reduce the likelihood of heart attacks and strokes among certain high-risk patients.

["]It will probably soon be as common to have one's homocysteine level checked as it is now to have one's cholesterol level checked," said Dr. Malinow of the Oregon Health Sciences University in Portland, a joint author of the Science Advisory.

Competitive Technologies, Inc. (Amex: CTT - news) supported and patented the technology now licensed to laborato-

ries performing in excess of 75% of homocysteine tests in the United States.

"We first became involved with this technology in the mid-1980s when we began working with the team from the University of Colorado and Columbia University that made important discoveries in the homocysteine area. We're now very happy to see it come to fruition," said Competitive Technologies' President Frank McPike. "We have always known that it takes many years to bring important medical technologies into the market, but we think the investment is worthwhile, especially when it delivers something that can actually save lives like this test. We plan to continue to work long and hard so we can keep bringing other equally useful and important technologies to the market.

Cardiovascular disease is the leading cause of death in the United States, killing one American every 33 seconds, a cost to the American economy of $150 billion a year. A test for high homocysteine blood levels may help reduce that number because elevated levels of homocysteine can be reduced with a relatively simple change in diet. Because high levels of homocysteine directly correlate to low levels of folic acid and vitamins B12 and B6, in addition to screening, the Science Advisory also urges all Americans to increase their intake of foods containing folic acid and vitamins B12 and B6 such as leafy green vegetables, fruits, and legumes.

At normal levels, homocysteine is an amino acid used by the body to help build and maintain body tissue. Too much homocysteine, however, causes blood platelets to clump together and damage the lining of arteries. That, in turn, can lead to heart attacks and strokes.

Because of the increasing importance associated with identifying homocysteine levels, the number of homocysteine tests performed could top 100 million per year. CTT's share of retained royalties from its homocysteine licensees during the first fiscal quarter of 1999 has already increased over 200% from the corresponding period of 1998. The average price of a test is $53. In addition to cardiovascular disease, high levels of homocysteine have also been linked to Alzheimer's

disease, Chronic Fatigue Syndrome and Rheumatoid Arthritis. CTT's U.S. Patent No. 4,940,658 expires in 2007.

Competitive Technologies is a global leader in the identification, development and commercialization of innovative technologies in the areas of life sciences, physical sciences and digital technologies. Competitive Technologies' specialized expertise and experience make it a valuable partner for companies of all sizes within the area of technology commercialization. CTT has evaluated more than 25,000 technologies and has been responsible for closing hundreds of license agreements.

Important CTT clients and licensees include: SONY (NYSE: SNE - news), Lucent Technologies (NYSE: LU), Matsushita Electric Industrial (NYSE: MC), and Ribozyme Pharmaceuticals, Inc. (Nasdaq: RZYM) among others. Competitive Technologies, Inc. is based in Fairfield, CT with affiliates in Osaka, Japan and London, England.

Statements about the Company's future expectations included development and regulatory plans, and all other statements in this document other than historical facts are "forward-looking statements" with the meaning of applicable Federal Securities laws and are not guarantees of future performance. These statements involved risks and uncertainties related to the market acceptance of and competition for the Company's licensed technologies and other risks and uncertainties inherent in CTT's business. These are set forth in Item 1 of the Company's Form 10-K for the year ended July 31, 1998. Other factors may also be described in CTT's filings with the SEC and are subject to change at any time. The Company's actual results could differ materially from these forward-looking statements.

Defendant's Exhibit AI

COMPETITIVE TECHNOLOGIES
1960 Bronson Road
Fairfield, CT 06430
(203) 255-6044

Releases

CTT's Homocysteine Technology Hits Main Street

- American Heart Association Alerts Doctors to Screen High-Risk Patients

- Available Today, Homocysteine Test May Become as Common as Cholesterol Test

FAIRFIELD, CT. (January 5, 1999)—After a year of promoting its homocysteine technology, **Competitive Technologies, Inc. (Amex: CTT)** is seeing its hard work pay off. Competitive Technologies, Inc., a global leader in technology commercialization, holds the patent which covers the performance of any test used to determine elevated homocysteine levels. The number of those tests may now be about to rise dramatically.

Scores of medical studies reveal that high levels of homocysteine may indicate a greater risk of vascular disease. In the wake of those studies, the American Heart Association (AHA) has released a Science Advisory urging doctors to immediately begin screening high-risk patients with a personal or family history of heart disease. The advisory will be featured in the upcoming January 5-12, 1999, issue of Circulation: Journal of the American Heart Association.

Though the number of homocysteine tests has been rising rapidly over the past year, they may increase even more quickly now. "It will probably soon be as common to have one's homocysteine level checked as it is now to have one's cholesterol level checked," said Dr. Malinow of the Oregon

Health Sciences University, a joint author in the AHA Science Advisory.

If that prediction proves true, the number of homocysteine tests could approach the level of cholesterol tests which has been estimated between 100 and 125 million tests per year in the United States alone. An estimated 20 million Americans, more than one of every three people with cardiovascular disease, have high levels of homocysteine.

"The American Heart Association's recommendation is important news," said CTT President Frank McPike. "Heart attacks kill more Americans than any other disease, and this recommendation certainly confirms the importance of homocysteine testing as a tool in the battle to reduce heart disease. This test is available today and we now expect physicians to increasingly encourage their patients who are at risk for heart disease to regularly monitor their homocysteine levels."

CTT believes it is now positioned to collect royalties on at least 75% of all homocysteine tests performed in 1999. According to McPike, CTT's retained royalties from its homocysteine licensees during the first quarter of fiscal 1999 has already increased more than 200% over the corresponding period in 1998, with the average price of a test being approximately $53. In addition to collecting royalties on more tests in 1999, CTT expects to increase its market share by targeting smaller diagnostic laboratories during the next six months.

CTT, which identifies and invests in incubator-stage technologies in return for licensing fees, royalties or equity, first became involved in homocysteine during the mid-1980's. The technology resulted from research performed at the University of Colorado by Drs. Robert H. Allen, Sally P. Stabler, and the late Dr. John Lindenbaum of Columbia University. In addition to cardiovascular disease, high levels of homocysteine have been linked to Alzheimer's disease, Chronic Fatigue Syndrome and Rheumatoid Arthritis. CTT's U.S. Patent No. 4,940,658 expires in 2007.

Competitive Technologies is a global leader in the identification, development and commercialization of innovative technologies in the areas of life sciences, physical sciences and digital technologies. Competitive Technologies' specialized expertise and experience make it a valuable partner for companies of all sizes within the area of technology commercialization. CTT has evaluated more than 25,000 technologies and has been responsible for closing hundreds of license agreements.

Important CTT clients and licensees include: SONY (NYSE: SNE), Lucent Technologies (NYSE: LU), Matsushita Electric Industrial (NYSE: MC), and Ribozyme Pharmaceuticals, Inc. (Nasdaq: RZYM) among others. Competitive Technologies, Inc. is based in Fairfield, CT with affiliates in Osaka, Japan and London, England.

Statements about the Company's future expectations included development and regulatory plans, and all other statements in this document other than historical facts are "forward-looking statements" with the meaning of applicable Federal Securities laws and are not guarantees of future performance. These statements involved risks and uncertainties related to the market acceptance of and competition for the Company's licensed technologies and other risks and uncertainties inherent in CTT's business. These are set forth in Item I of the Company's Form 10-K for the year ended July 31, 1998. Other factors may also be described in CTT's flings with the SEC, and are subject to change at any time. The Company's actual results could differ materially from these forward-looking statements.

Defendant's Exhibit AM

The Lancet, December 27, 1969

HOMOCYSTINURIA AND ORGANIC ACIDURIA IN A PATIENT WITH VITAMIN-B_{12} DEFICIENCY

SIR,—The letter of Dr. Shipman and his colleagues (Sept. 27, p. 693) suggesting genetic linkage of homocystinuria and the intrinsic-factor-deficiency type of pernicious anemia to a G chromosome prompts us to report our finding of homocysteine in the urine of a patient with Imerslund's syndrome – i.e., familial pernicious anemia and proteinuria. (In this syndrome the malabsorption of vitamin B_{12} occurs in the presence of intrinsic factor.)

Our patient, a 10-year-old White boy, was taking oral vitamins when he was referred to us because of nausea, vomiting, malaise, proteinuria, anemia, and ataxia. He was lethargic and pale. The glossal papillae were strophic, there were fissures at the angles of the mouth, and the liver was enlarged. He was ataxic, and position and vibration sense were impaired. Hemoglobin was 8·2 g. per 100 ml.; hematocrit 24%; red-blood-cell count 2,190,000 per c.mm.; reticulocytes 0·7%; platelet-count 237,500 per c.mm. The blood-film showed macrocytes (M.C.V. 100 c.mm., M.C.H. 37·9 µg., M.C.H.C. 35%) and hypersegmented neutrophils. Bone-marrow was megaloblastic. Serum glutamic-oxaloacetic and glutamic-pyruvic transaminases (S.G.O.T. and S.G.P.T.) and lactic-dehydrogenase (L.D.H.) were raised. Alkaline phosphatase and bilirubin were normal. Serum-carotene was 21·5 µg. per 100 ml.; serum-B_{12} was less than 50 pg. per ml. Schilling test: 0·2% of orally administered vitamin B_{12} was excreted in 24 hours, and with intrinsic factor 1·1% was excreted. Gastic analysis showed free acid which increased after betazole ('Histalog'). A gastric biopsy specimen and D-xylose absorption were normal. Aminoacid and organic-acid levels are shown in the accompanying table.

Two weeks after parenteral vitamin B_{12} treatment (total 3 mg.), the hemoglobin rose, and neurological function improved. The liver was no longer enlarged. At this time, urinary methylmalonic acid, fumaric acid, and homocystine were not measurable by the methods used.

The vitamin-B_{12} malabsorption in this patient appears to have a different genetic basis from that in the case reported by Dr. Shipman and his colleagues, yet homocystine was present in the urine in significant amounts. We interpret the homocystinuria in our case, like the methylmalonic aciduria, as being secondary to vitamin-B_{12} deficiency, an effect found in the vitamin B_{12} metabolic error reported by Mudd et al. This view was strengthened when urinary homocystine, cystine-homocystine disulfide, and methylmalonic acid promptly fell to normal after treatment with vitamin B_{12}. It is of interest that other compounds in the citric acid cycle—namely, α-ketoglutaric and *cis*-aconite acid—appeared in large amounts after treatment with parenteral B_{12}. This effect is being studied.

Further studies of the case of Dr. Shipman and his colleagues will be needed to prove their interesting hypothesis. In the meantime we wish to point out that significantly increased quantities of homocystine may be found in the urine of patients with pernicious anemia due to any one of several causes, and the homocystinuria may, as in the case we report here, be due to vitamin-B_{12} deficiency.

This work was supported in part by NIH grant RR-61 and GRS grant FR-5365.

J. G. Hollowell, Jr.
W. Knowlton Hall
Margaret E. Coryell
James McPherson, Jr.
Dorothy A. Hahn

Departments of Pediatrics
and Biochemistry,
Medical College of Georgia,
Augusta, Georgia 30902.

Defendant's Exhibit AW

Invited Review

March-April 1977

Volume 273 Number 2

Homocystinuria: pathogenetic mechanisms

ANTHONY J. GRIECO

Abstract: Homocystinuria with elevated plasma homocysteine and methionine levels is the result of deficient activity of cystathionine synthetase, the enzyme catalyzing conversion of homocysteine to cystathionine. It is inherited as an autosomal recessive trait with a worldwide distribution. The major clinical manifestations result from the elevated plasma homocysteine level. The excitotoxic effect of homocysteic acid accounts for mental retardation and seizures. Interference with collagen cross-linking by sulfhydryl groups of homocysteine causes ectopia lentis and skeletal deformities. Sulfation factor-like effects contribute to disruption of vascular endothelium, which is followed by platelet thrombosis and widespread arterial and venous occlusions. Low methionine homocystinuria, with deficient remethylation of homocysteine, results from deranged vitamin B_{12} metabolism and from deficient 5,10-methylene-tetrahydrofolate reductase. Administration of azaribine produces homocystinuria by a mechanism not yet elucidated.

Defendant's Exhibit BA

The New England Journal of Medicine

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Volume 299 August 17, 1978 Number 7

A SYNDROME OF METHYLMALONIC ACIDURIA, HOMOCYSTINURIA, MEGALOBLASTIC ANEMIA AND NEUROLOGIC ABNORMALITIES IN A VITAMIN B_{12}-DEFICIENT BREAST-FED INFANT OF A STRICT VEGETARIAN

Marilyn C. Higginbottom, M.D., Lawrence Sweetman, Ph.D., and William L. Nyhan, M.D., Ph.D.

Abstract: We studied a six-month old infant with severe megaloblastic anemia, coma and hyperpigmentation of the extremities. He was found to have methylmalonic aciduria (79 μmol per milligram of creatinine) and homocystinuria (0.85 μmol per milligram of creatinine) Additional biochemical abnormalities included cystathioninuria, glycinuria, methylcitric aciduria, 3-hydroxypropionic aciduria and formic aciduria. The concentration of vitamin B_{12} in the serum was 20 pg per milliliter. This severe nutritional deficiency was a consequence of inadequate intake, for the infant was exclusively breast-fed by a strictly vegetarian mother who manifested methylmalonic aciduria. Our observations emphasize the importance of educating strict vegetarians about the deficiency of vitamin B_{12} in their diets and the importance of vitamin B_{12} supplementation. (N Engl J Med 299:317-323, 1978)

The increasing rarity of nutritional-deficiency disease may create problems in medical diagnosis and management for physicians in developed countries. Vegan diets – those from which animal proteins are strictly excluded – have become increasingly popular. Although rich in many vitamins, these

diets are deficient in vitamin B_{12}. In the infant described below, striking dysfunction of the hematopoietic and central nervous systems resulted from nutritional deficiency of vitamin B_{12}. The infant had been exclusively breast-fed by a strict vegetarian mother. The presentation of the infant suggested an inborn error of metabolism, and he was found to have methylmalonic aciduria and homocystinuria. Both the biochemical and the clinical abnormalities resolved after therapy with vitamin B_{12}. These observations emphasize the need for vitamin B_{12} supplementation in vegan women who breast-feed their infants or for supplementation for the infants themselves.

* * * *

Defendant's Exhibit BE

Clinical Science (1981) 61, 743-749

Homocysteine in the plasma of renal transplant recipients: effects of cofactors for methionine metabolism

D. E. L. WILCKEN, VATSALA J. GUPTA AND A. K. BETTS

The Department of Medicine, The Prince Henry Hospital, Sydney, New South Wales, Australia

(Received 26 November 1980/16 March 1981; accepted 11 June 1981)

Summary

1. Homocysteine which is formed during the metabolism of methionine is readily oxidized and is measured by the amino acid analyzer as cysteine-homocysteine mixed disulphide and homocystine. We measured plasma amino acid concentrations after an overnight fast in 27 stable long-term renal transplant recipients and 25 age and sex-matched normal subjects with particular emphasis on sulphur-containing amino acids.

2. Plasma cysteine-homocysteine mixed disulphide was increased in the patients (mean 6·0 ± SD 3·2 μmol/l; normal 3·1 ± 0·9 μmol/l. $P < 0·001$) and homocysteine was detectable in low concentration (<1·0 μmol/l) in 24; the elevation in cysteine-homocysteine was related to serum creatinine ($r = 0·60$. $P < 0·002$). Cystine was also increased (91·6 ± 29·3 μmol/l; normal subjects 64·0 ± 16·7 μmol/l, $P < 0·001$), but methionine concentrations were normal.

3. When pyridoxine, folic acid and vitamin B_{12}, cofactors for homocysteine metabolism, were administered sequentially to 11 arbitrarily selected transplant recipients cysteine-homocysteine decreased from 7·3 ± 2·1 to 4·3 ± 0·8 μmol/l ($P < 0·001$) and homocystine became undetectable.

The response coincided with the giving of folic acid and occurred without alteration in serum creatinine and with normal serum folate and vitamin B_{12} concentrations.

4. In eight patients in whom pretreatment erythrocyte folate was measured, folic acid therapy reduced cysteine-homocysteine from 9·0 ± 3·1 to 5·4 ± 1·6 μmol/l over a 4 week period ($P < 0.001$), the largest response being in the one patient with subnormal erythrocyte folate; values were in the low-normal or normal range in the other seven.

5. We conclude that plasma homocysteine is increased in renal transplant recipients when serum creatinine is only moderately elevated and that the homocysteine concentrations are decreased by treatment with folic acid, suggesting that both reduced homocysteine excretion and relative shortages of folic acid are responsible.

Key words: amino acids, cysteine-homocysteine mixed disulphide, cystine, folic acid, homocysteine, homocystinuria, pyridoxine, renal failure, vascular disease.

* * * *

Defendant's Exhibit BF

Journal of the Royal Society of Medicine

Volume 75, August 1982

Vitamin B_{12} deficiency in a breastfed infant of a mother with pernicious anemia

Hilary Hoey, MRCP DCH
Queen Elizabeth Hospital for Children, London E2

J. C. Linnell, PhD FRSC
Westminster Medical School, London SW1

V. G. Oberholzer, BA
B. M. Laurance, FRCP DCH
Queen Elizabeth Hospital for Children, London E2

Nutritional vitamin B_{12} (cobalamin) deficiency is rare in infants, although reports from Europe (Burgio *et al.* 1956. Gerbasi 1960) and India (Jadhav *et al.* 1962. Jathar *et al.* 1970) show that it can lead to severe megaloblastic anaemia together with neurological abnormalities. In America, infantile megaloblastic anaemia is more often the result of folate deficiency (Luhby 1959), though similar clinical effects have been observed in nutritional cobalamin deprivation (Higginbottom *et al.* 1978).

A case is now reported of a 14-month-old breastfed girl, presenting with severe neurological features, in whom the finding of cobalamin deficiency led to the diagnosis of pernicious anaemia in her mother. Treatment with hydroxocobalamin led to the child's complete recovery.

* * * *

Investigations:

* * * *

The routine blood biochemistry on admission was essentially normal. Results of haematological investigations

were as follows: Hb 9.4 g/dl. WBC 9.7 x 10^9/l with a marked neutropenia platelets 564 x 10^9/l. The blood film was macrocytic and bone marrow from the left posterior iliac crest was frankly megaloblastic. At this stage an EEG was markedly abnormal with gross generalized changes and a CAT brain scan showed abnormalities similar to those in diffuse cerebral atrophy. Methylmalonic acid (MMA) was first detected in the urine by routine chromatography and was later estimated as 1000 µg/mg creatinine (normal 0-5). Urinary cystathionine, homocystine and the mixed disulphide of cysteine-homocysteine also abnormally raised. While in the plasma levels of cystathionine and homocysteine were elevated but methionine was low. Taken together, these findings suggested a possible defect in cobalamin metabolism (Figure 1). The patient's serum total cobalamin was grossly low: 40 ng l by Euglena (normal 150-1000) and 46 ng l by radioisotopic assay (normal 130 950); total folate was also very low, serum folate being 0.4 µg l (normal 6.0-21) and red cell folate 11 µg l (normal 150 1000). In addition, her serum iron (6.2 µmol l: normal 6 16) and total iron binding capacity (57.8 µmol/l; normal 54 89) were at the lower limit of normal.

* * * *

Known metabolic defects of cobalamin metabolism are shown schematically in Figure 1. A cellular deficiency of MeCbl and AdoCbl leads to increased excretion of homocystine and MMA respectively. In the present case the low plasma level of MeCbl and total Cbl suggested either a dietary deficiency, malabsorption or a disorder of cobalamin transport. Selective cobalamin malabsorption (Imerslund-Gräsbeck syndrome) was unlikely since there was no proteinuria and a transport defect was excluded by the finding that TCI and TCII-binding were normal. Since the mother's milk contained only about one-tenth the lowest concentration of cobalamin normally present in breast milk and since this was the child's sole diet, a nutritional deficiency seemed the most likely. Unfortunately, the breast milk folate was not estimated, but both mother and child had low serum and red cell folate concentrations. Since SG was treated with folic acid simultaneously with OHCbl, one cannot be entirely

certain that a folate deficiency played no part in the progress of the disease. However, the finding of a low Schilling test and a haematological response to CNCbl in the mother strongly suggests that the child's primary deficiency was of cobalamins.

Defendant's Exhibit BQ

Moderate Homocysteinemia – A Possible Risk Factor For Arteriosclerotic Cerebrovascular Disease

Lars E. Brattstrom, M.D., Jan Erik Hardebo, M.D. and Bjorn L. Hultberg, M.D.

SUMMARY Highly elevated concentrations of homocysteine measured as homocysteine or cysteine-homocysteine mixed disulfide (MDS) are found in plasma and urine in subjects with inherited abnormalities of the methionine metabolism. These subjects have a high incidence of arteriosclerotic vascular complications during childhood. Homocysteine causes endothelial cell injury and cell detachment that initiates the development of arteriosclerosis. The present study demonstrates a significantly elevated mean plasma MDS concentration in 19 patients with arteriosclerotic cerebrovascular disease compared to 17 controls. Our findings suggest that moderate homocysteinemia might be a risk factor for arteriosclerotic cerebrovascular disease.

Stroke Vol 15, No 6. 1984

HOMOCYST(E)INEMIA/URIA IS usually secondary to deficiency of cystathionine β-synthase, a pyridoxal phosphate dependent enzyme to the transsulfuration pathway (fig. 1). It is an autosomal recessive inborn error of methionine metabolism. Homocysteinemia can also be due to a reduced capacity for homocysteine remethylation via the folate and cobalamine dependent transmethylation pathway. It is characterized by elevated concentrations of homocysteine and its two disulfides homocystine and cysteine-homocysteine mixed disulfide (MDS) in plasma and urine.

The main cause of morbidity and morality in homocysteinemic patients is progressive premature arteriosclerosis and associated thromboembolic complications. Histopathologically there are widespread arterial focal lesions with fibrous intimal plaques and medial fibrosis with fraying and

splitting of the internal elastic membranes. Homocysteine or its derivates are considered to cause these changes.

* * * *

Defendant's Exhibit BU

Folic Acid Responsive Postmenopausal Homocysteinemia

Lars E. Brattström. Björn L. Hultberg. and Jan Erik Hardebo

Homocysteinemia is associated with juvenile arteriosclerosis, recurrent thromboembolic complications and osteoporosis. Plasma homocysteine, measured as homocysteine-cysteine mixed disulfide (MDS), has in other than homocysteinemics been reported to be higher in patients with coronary heart or cerebrovascular disease than in controls, and higher in men than in premenopausal women. Here, in groups of normal men and normal premenopausal and postmenopausal women, we measured plasma MDS in the fasting state and four hours after a methionine load (100 mg/kg body weight), before and after four weeks of folic acid therapy at 5 mg daily. In their fasting plasma, postmenopausal women (n - 5) had significantly ($P < 0.05$) higher MDS concentrations than premenopausal women (n - 5) and younger men (n – 5). After the methionine load MDS concentrations in postmenopausal women rose markedly, reaching levels significantly higher than those in younger men ($P < 0.05$), and with no overlap with values in premenopausal women ($P < 0.01$), or in older men (n - 5, $P < 0.01$). Folic acid therapy resulted in substantial reductions (n - 15, $P < 0.01$) of MDS concentrations both before the methionine load (-31%) and after (-28%), though subjects had initially had normal concentrations of serum and erythrocyte folates. We speculate that moderate homocysteinemia might contribute to postmenopausal arteriosclerosis and osteoporosis. Should this prove to be the case, folic acid might be a useful prophylactic.

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METHIONINE, an essential amino acid containing sulfur is metabolized to cysteine by means of the transsulfuration pathway. Homocysteine constitutes the juncture between this pathway and the folate, cobalamin, and betaine dependent transmethylation cycle (Fig 1). Deficiencies of certain

enzymes involved in these pathways, will result in homocysteinemia, owing to the accumulation, in plasma and tissue, of homocysteine and its two disulfides–homocystine (homocysteine-homocysteine) and homocysteine-cysteine mixed disulfide (MDS).

Homocysteinemia is associated with juvenile arteriosclerosis, recurrent arterial and venous throboembolic manifestations, and osteoporosis. If untreated, more than 50% of affected individuals die before the age of 20 of myocardial infarction, stroke or pulmonary embolism. Experimental homocysteinemia in baboons has shown that homocysteine induces endothelial injury, arteriosclerosis, and thrombosis. Homocysteine also interacts with collagen synthesis, an interaction that may be significant in the development of osteoporosis.

Homocysteine concentrations, measured as MDS in plasma from men with ischemic heart disease and controls have been investigated in two studies by Wilcken et al. in one of which, though not in the other, they found significantly higher MDS concentrations in patients than in controls after a methionine load. They suggested that persistent moderate increases in plasma homocysteine might be a risk factor for arteriosclerotic coronary heart disease. In a recent study we measured plasma MDS in patients with carotid artery stenosis, TIAs or strokes, and found significantly higher ($P < 0.05$) concentrations in the patients both before and after a methionine load: female controls (> 50 years) tended to have higher values than males and younger females: three female controls were also given folic acid, 5 mg daily for four weeks, and then reinvestigated, a substantial reduction of the MDS concentrations being found in all three subjects both before and after the methionine load.

Before this study was begun, MDS concentrations in normal women and men had only been reported in young subjects, and to be significantly higher in men than in women. We therefore measured plasma MDS in groups of normal premenopausal and postmenopausal women, as well as in age-matched groups of normal men. The subjects were

investigated before and after a methionine load and reinvestigated after four weeks of folic acid therapy.

Defendant's Exhibit CN

CONFIDENTIAL

University of Colorado Health Sciences Center
Department of Medicine
Division of Hematology
Campus Box B170 School of Medicine
4200 East Ninth Avenue
Denver, Colorado 80262
(303) 270-8474

January 5, 1990

Dr. Malinow
505 N.W. 185th Avenue
Beaverton, OR 97006

Dear Dr. Malinow:

I enclose reprints of the work of Dr. Robert Allen and myself diagnosing vitamin B12 deficiency using serum levels of methylmalonic acid and homocysteine. The article in *Laboratory Management* describes the clinical problem in diagnosing this deficiency. It is not appropriate at the present time to state that because a patient has a serum cobalamin level >200 pg/ml, he has no chance of having B12 deficiency and, conversely, not every patient with a B12 level <200 pg/ml has B12 deficiency. Because of past literature showing that patients who receive folic acid in pharmacologic amounts who actually have vitamin B12 deficiency may have progression of neuropsychiatric deficits, I feel that a shotgun approach of giving folic acid to every patient with an elevated serum homocysteine is clearly not warranted. It can be difficult to specifically make the diagnosis of B12 deficiency in a patient with slight hematologic abnormalities or neuropsychiatric abnormalities

without associated hematologic abnormalities. I feel that any patient who had an elevated homocysteine should certainly have a methylmalonic acid level performed since if both levels are elevated, the patient has vitamin B12 deficiency or chronic renal failure. If a patient has isolated homocysteine elevation, then the possibilities still include B12 deficiency, occult alcoholism or antifol treatment (numerous drugs interfere with folate metabolism, i.e. dilantin, tegretol, methotrexate, sulfa drugs, etc.). It would seem likely that the heterozygous state for cystathionine beta synthase deficiency would probably be less represented in the general population than these other clinical situations which would also cause an increase in serum homocysteine. This would be particularly true in elderly populations since, as shown in our preliminary data in the enclosed abstract (submitted to the American Geriatrics Society), there is a high prevalence of unsuspected vitamin B12 deficiency in elderly outpatients, perhaps as high as 14%.

We plan to discuss studies on standardizing the homocysteine assay with Dr. Refsum at the Vermont meeting of B12, folate and 1-carbon metabolism this summer, assuming she will attend.

Sincerely,

Sally P. Stabler, M.D.

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CONFIDENTIAL

HYPERHOMOCYSTEINEMIA: A COMMON AND TREATABLE CAUSE OF VASCULAR DISEASE AND NEURAL TUBE DEFECTS

Medical Grand Rounds — September 13, 1995

SALLY P. STABLER, M.D.

Learning Objectives

1. Know that homocysteine is a sulfhydryl-containing amino acid and it's metabolic role.

2. Know that homocysteine levels depend on vitamin B_{12}, folate, B_6 or renal status.

3. Learn important aspects for critiquing in vivo and in vitro studies of hyperhomocysteinemia.

4. Be aware that genetic polymorphisms may interact with environmental factors to produce hyperhomocysteinemia.

* * * *

Homocysteine Metabolism

Homocysteine can be methylated to form methionine by methyltetrahydrofolate in a reaction requiring methyl-B_{12} as a cofactor or condensed with serine to form cystathionine which is a precursor of cysteine in reactions that are dependent on vitamin B_6 (pyridoxical-5'-phosphate). The former reactions are referred to as transmethylation and the latter as transsulfuration. The pathway below shows the structures of the compounds involved.

* * * *

Hyperhomocysteinemia

Hyperhomocysteinemia is a term used to describe elevated total homocysteine levels in serum or plasma. The term homocystinuria is reserved for the genetic disorder caused by a deficiency of cystathionine-B-synthase. Hyperhomocysteinemia can be caused by deficiencies of vitamin B_{12} and folate and possibly vitamin B_6, drugs that interfere with folate, B_6 or B_{12} metabolism, by congenital defects of the enzymes involved in folate, B_{12} and B_6 related enzymes, and by chronic renal insufficiency. Vitamin B_{12} is a required cofactor in another pathway which converts L-methylmalonyl CoA to succinyl CoA. In defects in vitamin B_{12} metabolism, methylmalonic acid levels increase together with serum total homocysteine (Stabler 1986, Allen 1993). If methylmalonic acid levels are increased with total homocysteine then the defect is related to B_{12} metabolism versus folate metabolism. Even very mild degrees of renal failure can lead to increases in both serum total homocysteine and methylmalonic acid, and subjects with ESRD and those on dialysis have fairly marked elevations of homocysteine. The tables below list the common defects related with hyperhomocysteinemia.

DRUGS	VITAMINS	GENETIC DEFECTS	MISCELL-ANEOUS
Anti-folate drugs	Vitamin B_{12} Deficiency	Cystathionine B-synthase Deficiency (homocystinuria)	Renal Insufficiency
Methotrex-ate	Folate Deficiency	Vitamin B_{12} Defects in:	Psoriasis
Pyrimeth-amine	Vitamin B_6 Deficiency	Absorption	Leukemia
Sulpha Drugs		Transport	
Triam-terene		Coenzyme formation	
Phenytoin		Methionine Synthase Defects	
Carbam-azepine		Folate Defects in:	
Alcohol		Absorption	
N_2O		Transport	
		5,10-Methylenete-trahydrofolate Reductase Deficiency	

* * * *

Defendant's Exhibit JB

Annu Rev Medicine 1998 49 31-62
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HOMOCYSTEINE AND CARDIOVASCULAR DISEASE

H. Refsum, MD and P. M. Ueland, MD
Department of Pharmacology,
University of Bergen, Bergen, Norway.
e-mail: helga.refsum@farm.uib.no; per.ueland@ikb.uib.no

O. Nygård, MD and S. E. Vollset, MD, Dr.PH
Division for Medical Statistics,
Department of Public Health and Primary Health Care,
University of Bergen, Bergen, Norway;
e-mail: ottar.nygard@smis.uib.no;
stein.vollset@smis.uib.no

KEY WORDS: homocysteine, vascular disease, folic acid, vitamin B12, vitamin B6

ABSTRACT

An elevated level of total homocysteine (tHcy) in blood, denoted hyperhomocysteinemia, is emerging as a prevalent and strong risk factor for atherosclerotic vascular disease in the coronary, cerebral, and peripheral vessels, and for arterial and venous thromboembolism. The basis for these conclusions is data from about 80 clinical and epidemiological studies including more than 10,000 patients. Elevated tHcy confers a graded risk with no threshold, is independent of but may enhance the effect of the conventional risk factors, and seems to be a particularly strong predictor of cardiovascular mortality. Hyperhomocysteinemia is attributed to commonly occurring genetic and acquired factors including deficiencies of folate and vitamin B12. Supplementation with B-vitamins, in particular with folic acid, is an efficient, safe,

and inexpensive means to reduce an elevated tHcy level. Studies are now in progress to establish whether such therapy will reduce cardiovascular risk.

INTRODUCTION

The total homocysteine (tHcy) level in plasma or serum is a sensitive indicator of vitamin B12 and folate deficiencies (1). It is related to pregnancy complications (2), neural tube defects (3), mental disorders (4, 5), and cognitive impairment in the elderly (6, 7). Furthermore, data from about 80 clinical and epidemiological studies provide ample evidence that an elevated tHcy level is a common cardiovascular risk factor in the general population (8-10).

Determinants of the tHcy Level

Determinants of tHcy include genetic and acquired factors as summarized in Table 1.

AGE, SEX, AND RENAL FUNCTION Women have lower tHcy than men, and tHcy increases with age (37, 53, 54). This may partly be due to differences in vitamin status (55), but also to the influence of sex hormones. Plasma tHcy, levels increase after menopause (53, 56), which may explain the steeper age-related increase in women compared with men (54). The sex difference may also be related to stoichiometric formation of Hcy in connection with the creatine/ creatinine synthesis that is proportional to muscle mass, and therefore higher in men than in women (57).

Renal function is a strong determinant of the tHcy level (58, 59). This is probably related to Hcy clearance via renal metabolism (60) rather than urinary excretion, which is minor (52, 61). The physiologic decline in renal function may partly explain the age effect (62, 63).

LIFESTYLE Dietary intake of vitamin B6, B12, and folate is inversely correlated to plasma tHcy (55). Smoking and caffeinated coffee consumption cause a shift of the distribution towards higher tHcy values, whereas physical activity is associated with low tHcy levels (54, 64). Notably, the effect of these lifestyle factors on the tHcy level seems to be more

pronounced in women than in men (37, 54, 64). Chronic, high ethanol consumption is associated with elevated tHcy levels (65), possibly through its effect on vitamin status. In contrast, a moderate consumption seems to be associated with a lower tHcy level (66).

GENETIC DETERMINANTS Homocystinuria usually refers to the inborn errors of Hcy metabolism associated with severe hyperhomocysteinemia. Homozygosity for CBS deficiency is the most common cause, with a birth prevalence of 1/300,000, but with marked geographic differences (15). Rare forms of homocystinuria include severe defects of MTHFR (67) and impaired Hcy remethylation due to inborn errors of cobalamin metabolism (68).

Heterozygosity for CBS deficiency is present in < 1 % of the general population (15). These subjects usually have a normal fasting tHcy level, but the PML tHcy level may be elevated (43, 44). Recent genetic studies have shown that heterozygosity for CBS deficiency occurs only sporadically in vascular patients (14, 69, 70) and suggest that this mild genetic defect is not a frequent cause of hyperhomocysteinemia in these patients.

The common C677T mutation in the MTHFR gene shows ethnic differences with a high allele frequency of about 40% (10% TT genotype) in Caucasians (71), whereas it is almost absent in African-Americans (72). This polymorphism causes reduced enzyme activity and thermolability and predisposes to moderate (15-30 μM) and intermediate (30-100 μM) hyperhomocysteinemia under conditions of impaired folate status (29, 73, 74). A low daily dose (0.2 mg) of folic acid will probably enable maintenance of a normal tHcy level in most of these subjects (73).

Table 1 Determinants of the plasma total homocysteine level

	Effect	Reference(s)
Genetic factors		
Homozygosity for CBS defects	↑↑↑	15.80
Homozygosity for MTHFR defects	↑↑↑	81.82
Cobalamin mutations (C, D, L, I, G)	↑↑↑	68.83
Down's syndrome	↓	84
Thermolabile MTHFR	↑	14, 73, 74
Heterozygosity for CBS defects[1]	↑	85
Heterozygosity for MTHFR defects	↑	81, 82
Physiologic determinants		
Increasing age	(↑)	53, 54
Male sex	(↑)	53, 54
Renal function, reduced GFR	(↑)	86
Increasing muscle mass	(↑)	57
Lifestyle determinants		
Vitamin intake	↓	55
Smoking	(↑)	54
Coffee consumption	(↑)	64
Ethanol consumption	↑↓	65, 66
Physical activity	↓	54
Clinical conditions		
Folate deficiency	↑↑	1, 75
Vitamin B12 deficiency	↑↑↑	1
Vitamin B6 deficiency[1]	↑	87
Renal failure	↑↑	59, 76
Hyperproliferative disorders	↑	88, 89
Hypothyroidism	↑	90
Drugs		
Folate antagonists (methotrexate)	↑	77

Vitamin B12 antagonists (nitrous oxide)	↑↑	91, 92
Vitamin B6 antagonists[1]	↑	45, 93
AdoHcy hydrolase inhibition	↓	94
Antiepileptic drugs	↑	8
Contraceptives, hormone therapy	↓	95-97
Aminothiols (acetylcysteine, penicillamine)	↓	78, 79
Others (L-dopa, cholestyramine, niacine)	↑	98-100

↓ = Reduction of the total homocysteine level; (↑) = increase within normal reference range; ↑, ↑↑, ↑↑↑ = moderate hyperhomocysteinemia (15-30 μM), intermediate hyperhomocysteinemia (30-100 μM), and severe hyperhomocysteinemia (>100 μM), respectively. AdoHcy = S-adenosylhomocysteine; CBS = cystathionine β-synthase; MTHFR = methylenetetrahydrofolate reductase.

[1]In subjects with vitamin B6 deficiency or mild defects in CBS, the fasting total homocysteine level is usually normal but the postmethionine load level is increased.

CLINICAL CONDITIONS AND DRUGS Folate or cobalamin deficiency are common causes of hyperhomocysteinemia in the general population (1, 75). Elevated tHcy levels are also observed in renal failure (59, 76), and in various other clinical conditions (Table 1) (9). Hyperhomocysteinemia is induced by certain drugs, especially those affecting the vitamins related to Hcy metabolism (77). Aminothiols, like penicillamine (78) and acetylcysteine (79), reduce the plasma tHcy level.

Reference Ranges

FASTING tHcy The normal range in adults is usually 5-15 μM, with a mean level of about 10 μM (Table 2) (32). Hyperhomocysteinemia is defined as a plasma tHcy > 15 μM and is denoted as moderate (15-30 μM), intermediate (30-100 μM) and severe (> 100 μM) hyperhomocysteinemia (101).

Reported reference ranges differ markedly (32). These variations are probably related to a skewed tHcy distribution toward higher values, varying defintions of the upper threshold, differences in sample handling and methodology, and variations in determinants of the (tHcy levels among different populations).

It has been suggested that reference ranges should be determined in a population with adequate vitamin status (102-104). Such individuals have markedly lower tHcy levels (with an upper limit of about 12 μM) than the general population. The 2.5-97.5 percentiles for 40-42-year-old subjects in the Hordaland population (n = 18,043) were 5.6-17.4 μM for women and 6.9-20.9 μM for men. The corresponding values for non-smokers with high folate intake and low coffee consumption were 4.7-11.4 μM and 6.3-13.1 μM, respectively (105).

Only sparse data exist on tHcy levels in children (88, 106-108). Recently, Tonstad et al found that tHcy levels in 8-12-year-old boys and girls are about half of that observed in adults. There was no sex difference, and the tHcy frequency distribution was nearly gaussian, with a mean tHcy level of 5.25 μM and a reference range (mean ± 2SD) of 2.9-7.6 μM (107). At puberty, tHcy increases markedly, and the distribution becomes skewed as in adult populations (108).

PML tHcy Relatively few investigations have addressed the reference range for PML tHcy levels (48, 53, 109, 110), and various definitions for an abnormal response have been used (9). Relative to the fasting level, the PML tHcy and the increase in tHcy measured after 4 to 6 h are usually about 3 and 2 times higher, respectively (Table 2). PML tHcy is higher in men than in women and increases with age, especially in women (109, 110).

Table 2 Fasting, postmethionine load (PML) and increase after loading in plasma total homocysteine level in the control group of the European Concerted Action Project on homocysteine and vascular disease (49)

	Percentile								
	2.5	5	10	20	50	80	90	95	97.5
	(μmol/L)								
All (n=800)									
Fasting	5.9	6.4	7.0	7.7	9.5	12.1	13.4	15.7	18.5
PML	17.4	19.2	21.5	24.2	29.9	38.0	43.7	51.3	58.1
Increase	10.4	11.6	13.1	15.4	19.8	27.3	31.6	37.2	42.8
Men < 45 years (n=232)									
Fasting	6.3	6.8	7.2	7.8	9.6	11.9	12.9	15.8	18.8
PML	17.3	19.0	20.9	23.8	29.6	39.8	47.5	56.4	60.9
Increase	10.4	11.4	12.3	15.2	19.3	28.2	34.1	39.1	44.7
Women < 45 years (n=135)									
Fasting	4.8	5.3	6.0	6.6	8.1	10.4	12.6	13.6	16.9
PML	16.0	16.6	17.9	20.0	26.0	34.1	40.2	44.7	48.2
Increase	8.9	9.9	11.3	13.1	17.8	23.9	30.1	32.1	34.9
Men > 45 years (n=338)									
Fasting	6.8	7.2	7.8	8.5	10.3	12.6	13.7	15.9	18.6
PML	21.0	22.0	23.6	25.7	31.0	38.0	42.9	50.3	57.9
Increase	12.8	13.8	14.9	16.2	20.6	26.6	30.1	35.5	41.7
Women > 45 years (n=95)									
Fasting	5.8	6.3	6.7	7.1	9.1	11.4	12.9	13.7	15.1
PML	16.8	19.6	21.5	24.0	31.2	36.9	42.4	50.1	54.2
Increase	10.1	12.0	13.7	15.3	21.4	28.2	33.3	40.3	43.2

HOMOCYSTEINE AND CARDIOVASCULAR DISEASE

History and Summary of Highlights up to 1995

Homocystinuria was described in 1962 in mentally retarded children (111, 112). About two years later, the defect in CBS was identified (113), and it was reported that such patients frequently had thromboembolic events (114, 115). Severe MTHFR deficiency (67, 116) and certain defects in intracel-

lular cobalamin metabolism (68, 117) were later reported to cause a similar clinical picture. In 1969, McCully described the vascular pathology of homocystinuria (117). He noted that thromboembolic disease was a characteristic feature of homocystinuria independent of the site of the metabolic defect, pointing to Hcy as the causal agent. This is the basis for his Hcy theory of atherosclerosis, which implies that moderately elevated tHcy may be a cardiovascular risk factor in the general population (118).

In 1976, Wilcken & Wilcken published the first report that coronary artery patients frequently have abnormal Hcy metabolism (119). For the following 15 years, there were only scattered reports (8, 9) on the relation between Hcy levels and coronary artery disease (120-122), cerebrovascular disease (123-125), peripheral artery disease (124, 126, 127), and venous thrombosis (128, 129). In the same period, the most important determinants of tHcy were identified, including age and sex (121, 130), renal function (76, 131), and folate and vitamin B12 status (75, 132). In 1988, Kang et al reported on thermolabile MTHFR and its relation to cardiovascular risk and hyperhomocysteinemia (27, 28).

Since 1990, there has been an exponential increase in the publication rate on tHcy and cardiovascular disease (Figure 2). This is related to the recognition of elevated tHcy as an independent cardiovascular risk factor (169). But equally important was the introduction of various assays for tHcy determination (32), which are more practical in the clinical setting and allow the use of stored blood samples. The first positive prospective studies on tHcy and coronary heart disease were reported in 1992 (170) and 1993 (171). One negative prospective study on myocardial infarction and stroke from Finland (172) caused some concern about the validity of the Hcy theory, but the hypothesis was later substantiated by several reports which indicated that tHcy is a risk factor for cardiovascular disease. In 1995, Selhub et al reported on a strong relation between tHcy and extracranial carotid-artery stenosis in the elderly (173), and a prospective study demonstrated that tHcy conveyed a graded risk for stroke in middle-aged British men (162). The same year, the

C677T mutation in the MTHFR gene was identified and proposed as a candidate risk factor for vascular disease (29).

In 1995, Boushey et al reviewed most studies on Hcy and cardiovascular disease. Their meta-analysis, based on 27 studies including about 4000 patients, showed that Hcy was an independent, graded risk factor for atherosclerotic disease in the coronary, cerebral and peripheral vessels (10). Since then, there have been about 40 additional studies on tHcy as a risk factor for cardiovascular disease and its complications (Table 3): the majority of them support the conclusions formulated by Boushey et al. The strongest evidence derives from ten prospective studies: Eight demonstrate an increase in risk of stroke (162, 174), coronary heart disease (163, 170), venous thrombosis (164), cardiovascular complications (166, 167) or mortality (168), whereas only two are negative (165, 172). Recent data have been reviewed and subjected to frequent editorial comments (175-179).

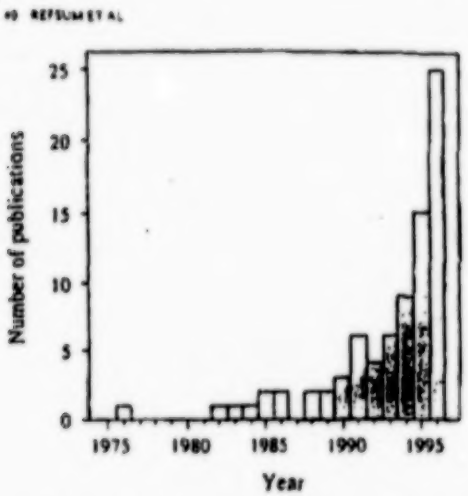

Figure. Number of clinical and epidemiological studies on homocysteine and cardiovascular disease in the years 1976 to 1996. Nine publications on methylenetetrahydrofolate and cardiovascular disease are included.

Hcy and Conventional Risk Factors

Hcy is one of more than 200 identified risk factors for cardiovascular disease (180). Thus, a frequently asked

question is whether the reported tHcy association is due to confounding with established factors.

A correlation between tHcy level and total, HDL or LDL cholesterol has been shown in some studies (9, 54, 62, 135, 163, 181). Two recent studies have smoking habits, blood pressure (Figure 3), and serum creatinine. Our data suggest that an increased tHcy level may contribute to acute thromboembolic events leading to death.

Mechanisms

Observations in homocystinuria patients, animal experiments, and in vitro studies have identified several potential sites where hyperhomocysteinemia may induce vascular lesions. These targets include connective tissue and smooth-muscle cells, platelets, endothelial cells, the vessel wall, blood lipids, coagulation factors, and nitric oxide.

In vitro (222) and in vivo (223) experiments suggest that Hcy promotes aggregation of platelets, but this has been contested (224, 225). Endothelial damage mediated through H_2O_2 production has been proposed (226-229), but cysteine induces similar effects, and the validity of these observations for in vivo atherogenesis has been questioned (23). Hcy increases DNA synthesis, growth, and cyclin A gene expression (231) in cultured vascular smooth muscle cells, and cyclin-dependent kinase expression in the aorta of rats (232). Oxidative modification of LDL by Hcy has been demonstrated in vitro (233, 234) but has not been observed in hyperhomocysteinemic patients (235, 236). Physiologic levels of Hcy may enhance the binding of lipoprotein(a) to fibrin (237), but cysteine and other thiols have a similar effect. High concentrations of Hcy in vitro activate factor V (238), reduce protein C activation (239, 240), inactivate the cofactor activity of thrombomodulin (241), suppress thrombomodulin (240) and anticoagulant heparan sulfate expression (242), and block tissue plasminogen activator binding to human endothelial cells (243). Hcy rapidly reacts with endothelium-derived relaxing factor/nitric oxide (NO) to form S-nitroso-Hcy, which acts as a potent antiplatelet agent and vasodilator. The formation of this adduct may attenuate

H_2O_2 production from Hcy and, thereby, protect against the atherogenic properties of Hcy. According to this model, vascular injury is caused by an imbalance between NO production from dysfunctional endothelial cells and the levels of Hcy (225). Notably, impaired endothelium-dependent vasodilatation associated with elevated tHcy has been demonstrated in vivo (244, 245). The possible etiologic mechanisms of Hcy in vascular disease have been summarized in recent review articles (225, 246).

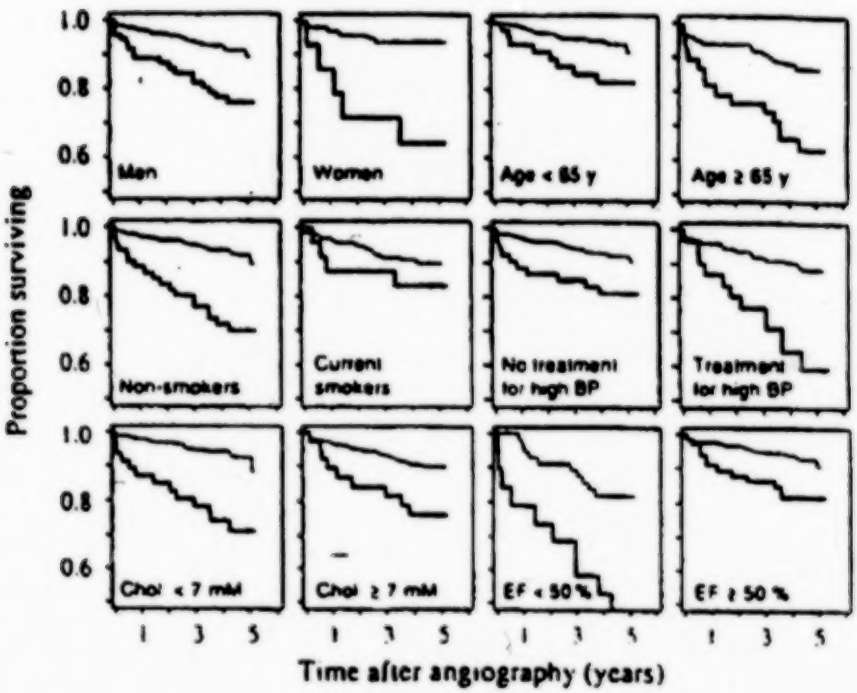

Figure 3 The relation between plasma total homocysteine (tHcy) and mortality Kaplan-Meier survival plots comparing patients with tHcy below (thin line) and above (thick line) 15 μM in various subgroups. The tHcy level was measured at the time of the angiography (168) BP, blood pressure; Chol., serum total cholesterol; EF left ventricular ejection fraction.

The data cited above show that there is no unifying hypothesis explaining the atherogenic and thrombogenic effects of circulating Hcy. This may reflect its diversity of effects,

but may also be due to flaws in study design or interpretation of data. In general, it is difficult to mimic the slow atherosclerotic effect by short-term in vitro studies. Another problem is related to the high millimolar concentrations of Hcy frequently used (229, 239, 243, 247, 248) that are 100- to 1000-fold higher than observed in moderate hyperhomocysteinemia (249). Moreover, the complex redox reactions involving the various Hcy forms and their relation to other aminothiols in vivo (31) contrast to the in vitro testing of a single Hcy species (249). Finally, the specificity of some Hcy effects should be questioned because they can be obtained by other thiols (230, 233, 250), in particular cysteine, which is the most abundant aminothiol in plasma, with a total concentration about 25-fold higher than tHcy (31).

HOMOCYSTEINE-LOWERING THERAPY

Increased intake of folic acid, vitamin B12, and B6 will probably reduce the tHcy level in nearly all individuals independent of their pretreatment tHcy level (251). Vitamin therapy partly prevents the vascular complications of homocystinuria (15), and use of vitamins is associated with lower risk of vascular disease in the general population (49). A high intake of fruits and vegetables, which are good sources of dietary folate, protects against cardiovascular disease (252), and an observational study suggests that vitamin B6 may delay the progress of coronary heart disease (253). However, it remains to be shown in randomized placebo-controlled clinical trials that a reduction of the tHcy level has an overall beneficial effect.

Vitamin and Drug Therapy

FOLIC ACID AND FOLATE INTAKE In 1988, Brattström et al showed that healthy subjects responded to a high does of folic acid (5 mg/d) with a marked reduction in their tHcy levels (254). Since then, several studies have demonstrated that 0.65-10 mg/d of folic acid alone or together with vitamin B12 and/or B6 reduce the fasting and PML tHcy level by 25-50%, both in healthy and in hyperhomocysteinemic subjects and in vascular patients (251, 255-257). Data on dose response are sparse, but no difference was found for 2.5

versus 10 mg/d inpatients with myocardial infarction (145) or for 0.5 versus 5 mg/d in healthy subjects (109).

Generally, a total folate intake from food and supplements below 200-250 μg/d is occasionally associated with hyperhomocysteinemia, whereas an intake of 300-400 μg/d usually ensures a normal to low tHcy level in the majority of the population (55, 258-260). A higher dose may be required to obtain a maximal tHcy reduction in subgroups such as patients with reduced renal function (261) or subjects with low folate status (73).

Folic acid is considered nontoxic and well tolerated for chronic use in high doses (262), but may mask the symptoms of vitamin B12 deficiency (see below).

VITAMIN B12 The effect of vitamin B12 on the tHcy level is modest with maximum 10-15% reduction (109, 254, 256), except in vitamin B12-deficient subjects (1). However, a low serum B12 level may prevent an optimal response to folic acid (73, 251). Moreover, there is high prevalence of vitamin B12 deficiency in elderly subjects (263). The concern that folic acid supplementation may alleviate hematological signs of B12 deficiency or even precipitate neuropathy has been thoroughly debated (10, 264-266). A daily vitamin B12 supplement of 200 μg/d can probably prevent the clinical symptoms of pernicious anemia (267).

VITAMIN B6 Oral treatment with pyridoxine up to 300 mg/d does not lower the fasting tHcy level in healthy subjects of vascular patients (251, 254, 257, 268). However, pyridoxine (10-250 mg/d) lowers an abnormal PML tHcy level in most patients, and, when combined with folic acid, nearly all obtain a normal PML tHcy level (45, 127, 255, 257, 269). Chronic use of vitamin B6 may precipitate peripheral neuropathy, but a daily dose of 100 mg or less is probably safe (270).

Defendant's Exhibit JC

AHA SCIENCE ADVISORY

Homocyst(e)ine, Diet, and Cardiovascular Diseases A Statement for Healthcare Professionals From the Nutrition Committee, American Heart Association

M. René Malinow, MD; Andrew G. Bostom, MD; Ronald M. Krauss, MD

Homocysteine and Diet

Homocysteine is a sulfur-containing amino acid, rapidly oxidized in plasma to the disulfides homocystine and cysteine-homocysteine (Figure 1). Plasma/serum total homocysteine, also termed homocyst(e)ine, is the sum of homocysteine in all 3 components. Figure 2 displays factors involved in the metabolism of homocysteine, including its metabolic relationship to methionine. Although dietary intake of total protein and methionine does not correlate significantly with blood homocyst(e)ine, a single dose of oral methionine (100 mg/kg body weight) can elevate homocyst(e)ine levels, and as described further below, this has been used as a diagnostic test to detect disordered homocyst(e)ine metabolism. Because variable changes in homocyst(e)ine levels have been observed postprandially, it is customary to obtain measurements in the fasting state. Normal levels of fasting plasma homocyst(e)ine are considered to be between 5 and 15 μmol/L. Moderate, intermediate, and severe hyperhomocyst(e)inemia refer to concentrations between 16 and 30, between 31 and 100, and >100 μmol/L, respectively.

Several vitamins function as cofactors and substrates in the metabolism of methionine and homocysteine (Figure 2). Folic acid and cyanocobalamin (vitamin B_{12}) regulate metabolic pathways catalyzed by the enzymes methylenetetrahydrofolate reductase (MTHFR) and methionine synthase, respectively, whereas pyridoxine (vitamin B_6) is a cofactor for cystathionine β-synthase. A number of studies have

shown inverse relationships of blood homocyst(e)ine concentrations with plasma/serum levels of folic acid, vitamin B_6, and vitamin B_{12}.

Administration of supplemental folic acid in doses between 0.2 and 15 mg/d can lower plasma homocyst(e)ine levels without apparent toxicity. On the basis of meta-analysis of 12 clinical studies; all but 1 of which was a placebo-controlled trial, it has been estimated that a 25% reduction in homocyst(e)ine concentration can be achieved with mean supplementation of 0.5 to 5.7 mg of folic acid per day; an additional 7% lowering has been observed after the addition of vitamin B_{12} (0.02 to 1 mg/d; mean, 0.5 mg). A recent report of the Food and Nutrition Board of the Institute of Medicine has recommended an upper limit of 1 mg/d folic acid on the basis of the possibility that higher doses may mask signs of vitamin B_{12} deficiency in some subjects. In overt cobalamin deficiency with intermediate and severe hyperhomocyst(e)inemia, vitamin B_{12} can normalize homocyst(e)ine concentration in ~70% of cases. In an open-label, uncontrolled study, vitamin B_6, at $\leq$250 mg/d was without effect in reducing basal homocyst(e)ine levels, but doses of 50 to 250 mg/d reduced homocyst(e)ine levels after a methionine-loading test by ~25%. Subsequently, a study that used a randomized, placebo-controlled, 2x2 factorial design demonstrated that 50 mg of vitamin B_6 per day independently reduced the post-methionine-loading increase in homocyst(e)ine levels by 22%. In a placebo-controlled study, a combination of multiple agents including folic acid (0.65 mg/d), vitamin B_6 (10 mg/d), and vitamin B_{12} (0.4 mg/d) was very effective in reducing homocyst(e)ine levels in patients with moderate or intermediate hyperhomocyst(e)inemia. It has been reported, however, that increased vitamin intake from food sources (1 mg of folic acid, 12.2 mg of pyridoxine, and 50 µg of cyanocobalamin per day) failed to maintain normal homocyst(e)ine levels attained previously by vitamin supplementation.

* * * *

Vitamin Intake, Homocyst(e)ine, and Cardiovascular Disease

In the case-control study of arterial diseases described above, folate deficiency was more common in cases, and plasma vitamin B_6 below the lowest 20th percentile (<23.3 nmol/L) for control subjects was associated with increased risk for vascular disease, ie, OR=1.84 (95% CI, 1.39 to 2.42). Of note, the relationship between vitamin B_6 and vascular disease was shown to be independent of homocyst(e)ine levels. Morrison et al demonstrated in the prospective Nutrition Canada Survey that the risk of fatal CAD was associated with low serum folate in 165 CAD deaths in subjects among 5056 men and women monitored for 20 years.

In a subset of subjects from the Atherosclerosis Risk In Communities study, carotid artery medial-intimal thickening was associated with high levels of homocyst(e)ine. Moreover, in a subset of subjects from the Framingham Heart Study, the stenosis was inversely proportional to reported intakes of both folic acid and vitamin B_6. Another analysis from the Framingham Study indicated that intake of fruits and vegetables was inversely related to incidence of stroke over a 20-year follow-up. Although homocyst(e)ine levels were not measured, the authors discussed, among other factors, the potential role of dietary folic acid in lowering homocyst(e)ine as a plausible mechanism involved in the protective effects of diet.

Users of multivitamins have been reported to have a reduced prevalence of CAD compared with nonusers. These findings have been extended in prospective observations conducted by Rimm et al in 80 082 women from the Nurses' Health Study. During a 14-year follow-up, the risk for fatal and nonfatal CAD was considerably lower among women who used multivitamins 4 to 7 times per week than among nonusers (risk ratio=0.76; 95% CI, 0.65 to 0.90) after multivariate adjustments. Caution must be exercised in interpreting observational studies, however, because of the possible effects of differences in unmeasured behaviors or risk factors that may be associated with

diet and vitamin intake. Moreover, the relationship of vitamin use to homocyst(e)ine levels was not evaluated in the study by Rimm et al.

Dietary Guidance With Regard to Homocyst(e)ine and Cardiovascular Disease

Population Guidelines

On the basis of the apparent relationship of plasma homocyst(e)ine to cardiovascular disease risk and the estimated influence of folic acid on homocyst(e)ine levels, Boushey et al suggested that a 350 μg/d increase in folic acid intake in men and a 280 μg/d increase in women could potentially prevent 30 500 and 19 000 vascular deaths annually in men and women, respectively. However, in the absence of prospective, placebo-controlled intervention trials of the effects of diet- or vitamin-mediated homocyst(e)ine reductions on incidence of cardiovascular disease, the clinical benefits of such interventions are unknown.

A recent report of the Food and Nutrition Board of the Academy of Sciences Institute of Medicine includes RDAs for folic acid, vitamin B_6, and vitamin B_{12} of 400 μg, 1.7 mg, and 2.4 μg, respectively, for nonpregnant, nonlactating individuals. Because a significant proportion of the population does not meet the current RDAs for folate intake, a reasonable population approach is to recommend an increase in the intake of foods containing those vitamins, ie, ready-to-eat fortified cereals, leafy green vegetables, fruits, and legumes as sources of folate; ready-to-eat fortified cereals, noncitrus fruits, poultry, beef, and certain vegetables (eg, artichoke, asparagus, beans, and cabbage) as sources of vitamin B_6; and beef, poultry, fish, and ready-to-eat fortified cereals as sources of vitamin B_{12} (see Reference 11 for more extensive information). These dietary modifications could result in elevated vitamin status and perhaps decreased homocyst(e)ine levels. However, because 10% to 30% of older people may malabsorb food-bound B_{12}, it is advisable for those older than 50 years to meet their RDA mainly by consuming food fortified with B_{12} or a B_{12}-containing supplement.

Moreover, on the basis of relative differences in bioavailability, the RDA guidelines equate 100 μg of folic acid from unfortified foods to 60 μg from fortified food and 50 μg from supplements. Because of methodological problems, food folate content in current databases may be significantly underestimated. Finally, prolonged heating or boiling, followed by discarding of water, or microwave heating may reduce folate content of food.

A complementary approach has been instituted as of January 1, 1998: the US Food and Drug Administration (FDA) has issued regulations requiring all "enriched" cereal grains to be fortified with folic acid at a concentration of 1.4 mg/kg grains to prevent neural tube birth defects. It has been estimated that this level of fortification would increase folic acid intake by 80 to 100 μg per day in women of childbearing potential and by 70 to 120 μg per day in adults older than 50 years. Whether this level of fortification will lower homocyst(e)ine concentrations in CAD patients needs to be determined. However, as described above, cereal products have been shown recently to lower homocyst(e)ine in CAD patients when they were fortified with 4 to 5 times the levels of fortification mandated by the US FDA.

Detection and Management of Elevated Fasting Homocyst(e)ine

* * * *

Thus, some researchers consider that a reasonable approach is to determine levels of fasting homocyst(e)ine in "high-risk patients," ie, in those with strong family history for premature atherosclerosis or with arterial occlusive diseases, particularly in the absence of other risk factors, as well as in members for their families, because hyperhomocyst(e)inemia in CAD seems to be transmitted, at least in part, through an autosomal dominant mechanism. Other conditions that may be associated with high homocyst(e)ine are advanced age, hypothyroidism, impaired kidney function, systemic lupus erythematosus, and certain

medications, eg, nicotinic acid, nitrous oxide exposure, theophylline, methotrexate, and L-dopa.

After confirmation of high homocyst(e)ine concentration, it is important to check the vitamin status owing to the inverse relationships reported between homocyst(e)ine and blood levels of folate, B6, and B12. A useful algorithm for the diagnosis of vitamin B12 deficiency, beyond the determination of blood levels of this vitamin, is described in Reference 11.

* * * *

AHA Nutrition Committee January 5/12, 1999

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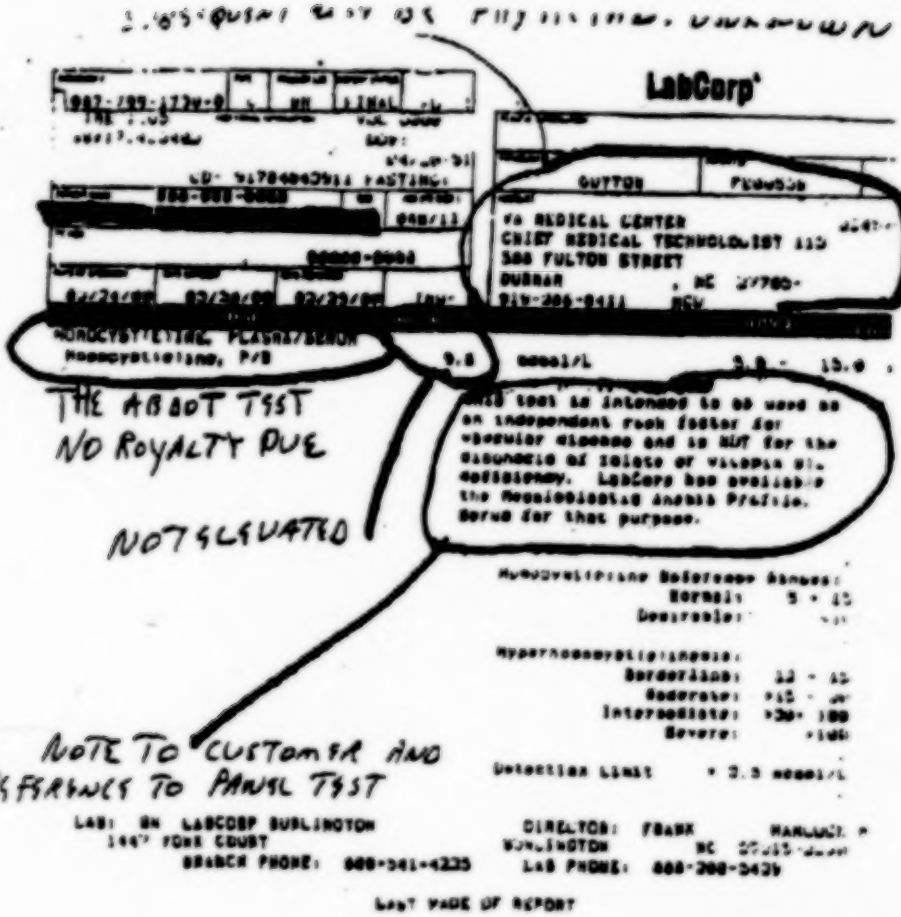
Defendant's Exhibit LT



LabCorp

[redacted]

GUTTON

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508 FULTON STREET
DURHAM , NC 27705-
919-286-0411 MCW

[redacted]

Homocystieline, P/B 9.8 mmol/L 5.0 - 15.0

This test is intended to be used as an independent rock factor for vascular disease and is NOT for the diagnosis of folate or vitamin B1 deficiency. LabCorp has available the Megaloblastic Anemia Profile. Serum for that purpose.

Homocystieline Reference Ranges:
Normal: 5 - 15
Desirable: [illegible]

Hyperhomocystielinemia:
Borderline: 12 - 15
Moderate: >15 - [illegible]
Intermediate: >30 - 100
Severe: >100

Detection Limit = 2.5 mmol/L

THE ABBOT TEST
NO ROYALTY DUE

NOT ELEVATED

NOTE TO CUSTOMER AND
REFERENCE TO PANEL TEST

LAB: BN LABCORP BURLINGTON
1447 YORK COURT
BRANCH PHONE: 800-541-4235

DIRECTOR: FRANK HANCOCK
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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLORADO

Civil Action. No. 99-Z-870

METABOLITE LABORATORIES, INC.,
a Colorado corporation, and
COMPETITIVE TECHNOLOGIES, INC.,
a Delaware corporation,

Plaintiffs,

vs.

LABORATORY CORPORATION OF AMERICA
HOLDINGS d/b/a LABCORP,
a Delaware corporation,

Defendant.

DECLARATION OF PETER WENTZ

I, Peter Wentz, declare and state as follows:

1. I am a resident of Elon College, North Carolina and have lived in Elon College since 1989. The following statements are based upon my own personal knowledge.

2. I am currently employed as Director of Toxicology for Defendant Laboratory Corporation of America Holdings, Inc. ("LabCorp") in Burlington, North Carolina. I have been employed by LabCorp (and its predecessor Roche Biomedical Laboratories, Inc.) at its Burlington lab since 1989. In my position as Director of Toxicology, I supervise approximately 45 LabCorp employees. I am responsible for ensuring that about 150 different tests conducted in the toxicology department are properly performed, including the tests licensed by Plaintiffs. LabCorp performs more than 2,000 different clinical tests. As a

clinical reference laboratory, LabCorp performs tests and provides results which assist physicians in diagnosing and treating diseases in their patients.

3. Prior to about August 1, 1998, LabCorp performed the single assay of homocysteine sold under test no. 706994 using the gas chromatography mass spectrometry method licensed to LabCorp by Metabolite. Beginning on or about August 1, 1998, LabCorp began performing the single assay of homocysteine sold under test no. 706994 using an immunoassay kit from Abbott Laboratories. Attached as Exhibit 1 hereto is a true and correct copy of a package insert from Abbott that describes its immunoassay method. This Abbott method does not use gas chromatography or mass spectrometry. Additionally, this Abbott method does not employ the steps recited in Claim 1 of the '658 patent of combining a sample containing homocysteine with an internal reference standard labelled with a suitable marker, measuring the relative amounts of labelled and unlabelled homocysteine with a mass spectrometer, or calculating the ratio of labelled and unlabelled homocysteine.

4. In some cases, LabCorp has included an assay of homocysteine under test no. 706994 in panels or superpanels containing other tests. For panels or superpanels performed after about July 31, 1998, which contained a homocysteine test no. 706994, those homocysteine tests were performed using the Abbott immunoassay method. None of the homocysteine tests (test no. 706994) included in panels or superpanels after about July 31, 1998 were performed using Metabolite's gas chromatography/mass spectrometry method.

5. Attached as Exhibit 2 hereto are copies of patient reports transmitting the results of assays of total homocysteine. In the Spring of 1999, language was included on LabCorp's homocysteine (test no. 706994) patient report to refer physicians to LabCorp's Megaloblastic Anemia profile test no. 706960 if the physicians were trying to diagnose a deficiency in cobalamin or folate.

This language is consistent with language that I proposed to Dr. Allen in 1992 when we first considered offering a single homocysteine test as a marker for cardiovascular disease.

6. Attached as Exhibit 3 hereto is a copy of the current Directory of Services page containing information on the single homocysteine test no. 706994. The information on that test refers the physician to LabCorp's Megaloblastic Anemia profile test (test no. 706960) to diagnose folate deficiency. LabCorp has paid and continues to pay royalties to plaintiffs on test no. 706960. The Megaloblastic Anemia profile test includes assays of four metabolites, methylmalonic acid. homocysteine, 2-methylcitric acid, and cystathionine. From the beginning, LabCorp has used the gas chromatography/mass spectrometry method licensed from Metabolite to assay each of the four metabolites, including homocysteine, for the Megaloblastic Anemia profile test. LabCorp continues to use the licensed gas chromatography/mass spectrometry method to assay each of the four metabolites, including homocysteine, for the Megaloblastic Anemia profile test.

7. LabCorp's Directory of Services contains a list of many of the more than 2,000 tests that LabCorp performs, including a description of each test to assist the physician in ordering tests. LabCorp listed the Megaloblastic Anemia profile test in its Directory of Services beginning in 1993 to inform physicians of the availability of the licensed test. Listing this test in LabCorp's Directory of Services would seem to be a benefit to Metabolite because LabCorp was paying Metabolite 27.5 percent of the revenue that LabCorp billed for each licensed test. Under that Agreement, Metabolite keeps 21.5 percent and pays 6.0 percent to CTI. LabCorp continues to pay a 27.5 percent royalty to Metabolite for each Megaloblastic Anemia profile test (test no. 706960) and other licensed tests performed by LabCorp that use Metabolite's gas chromatography/mass spectrometry method.

I declare under penalty of perjury of the laws of the United States of America that the foregoing is true and correct.

This the 2 day of August, 2000.

/s/ Peter Wentz

Peter Wentz

JURY INSTRUCTIONS

INSTRUCTION NO. 1

Now that you have heard the evidence, and the arguments of counsel, it becomes my duty to give you the instructions of the Court as to the law applicable to this case.

It is your duty as jurors to follow the law stated in the instructions of the Court and to apply the rules of law so given to the facts as you find them from the evidence in the case.

You are not to single out one instruction alone as stating the law, but must consider the instructions as a whole.

Neither are you to be concerned with the wisdom of any rule of law stated by the Court. Regardless of any opinion you may have as to what the law ought to be, it would be a violation of your sworn duty to base a verdict upon any other view of the law than that given in the instructions of the Court; just as it would be a violation of your sworn duty, as judges of the facts, to base a verdict upon anything but the evidence in this case.

Nothing which is said in these instructions is to be taken as an indication that the Court might have an opinion about the facts in the case, or what that opinion is. It is not the Court's function to determine the facts, but rather yours.

Justice through trial by jury depends upon the willingness of each individual juror to seek the truth as to the facts from the same evidence presented to all jurors; and to arrive at a fair verdict applying the same rules of law, as given in the instructions of the Court.

This case should be considered and decided by you as an action between persons of equal standing in the community, of equal worth, and holding the same or similar stations of life. A corporation is entitled to the same fair trial at your

hands as a private individual. All persons, including corporations, stand equal before the law, and are to be dealt with as equals in a court of justice.

INSTRUCTION NO. 2

I will now explain the claims and defenses of each party to the case and the law governing the case. Please pay close attention to these instructions. These instructions include both general instructions and instructions specific to the claims and defenses in this case. You must consider all the general and specific instructions together. You must all agree on your verdict, applying the law , as you are now instructed, to the facts as you find them to be.

The parties agree on the following facts. The Professors assigned their rights to plaintiff CTI (then called University Patents, Inc.). The Patent Office issued the '658 patent to CTI. CTI licensed the patent to plaintiff Metabolite. In turn, Metabolite sublicensed the patent to a company called Roche, which became defendant LabCorp through a merger. Therefore, there is now a sublicense agreement between Metabolite and LabCorp. Even though this is technically a sublicense agreement, it is titled "License Agreement."

Next I will read to you contentions of the parties on which they do not agree.

Plaintiffs make the following contentions: The license agreement requires LabCorp to pay royalties amounting to 27.5% on its performance of any homocysteine tests if LabCorp's actions in performing such tests would, but for the existence of the License Agreement, infringe any valid claim of the patent either contributory or by inducement. The license agreement contains Section 4.02 addressing termination by LabCorp with respect to particular tests. Under that Section 4.02, LabCorp may terminate the license agreement with respect to homocysteine tests if it finds a more cost-effective commercial alternative and its performance of that

alternative does not infringe a valid and enforceable claim of the patent. The patent is presumed valid.

LabCorp decided sometime before 1998 that it might avoid its royalty obligations under the license agreement by switching to a homocysteine test sold by a company called Abbott. A LabCorp employee named Dr. Wentz made the determination that LabCorp's performance of homocysteine tests using the Abbott system did not infringe a valid and enforceable claim of the Professor's patent because the Abbott system is not by GCMS. On that basis, LabCorp terminated the license agreement with respect to the homocysteine-only test and stopped paying royalties on that test.

However, Dr. Wentz by his own admission is not competent to interpret patents, and knows nothing about the concepts of contributory infringement and infringement by inducement. In point of fact, LabCorp's performance of homocysteine-only tests using the Abbott System does constitute contributory infringement and infringement because claim 13 is not limited to GCMS and there are no substantial uses of the homocysteine-only tests other than to detect B_{12} or folate deficiencies. Further, LabCorp induces infringement of claim 13 by encouraging physicians to assay for total homocysteine and to correlate the results with B_{12} or folate deficiencies.

Therefore, LabCorp's termination of the license agreement and discontinuance of its royalty payments with respect to that test constitutes breach of its contract with Metabolite. And LabCorp's ongoing performance of these tests following its termination of the license agreement with respect to those tests, constitutes contributory infringement and infringement by inducement of the patent owned by CTI.

Monitoring patients for vascular disease is not a use of homocysteine testing separate from detecting vitamin deficiencies; this is evident from the fact that all parties agree that the standard treatment for elevated homocysteine in heart

disease patients is the same as the standard treatment for all other patent. The standard treatment is vitamin supplements.

Defendant makes the following contentions: Defendant LabCorp admits that it is licensed under the '658 patent by Metabolite and does not have any liability for patent infringement. LabCorp denies that it owes plaintiffs any additional royalties under the license agreement. LabCorp did not terminate the license agreement or any portion of it with respect to homocysteine tests because LabCorp continues to perform certain homocysteine tests by the licensed gas chromatography/mass spectrometry method and continues to pay royalties on those homocysteine tests to plaintiffs. Defendant does not owe Metabolite a 21.5% royalty for performing the Abbott single homocysteine test because the assay is not a Licensed Assay as defined by the Licensed Assay and does not use Metabolite's technology.

LabCorp began using the Abbott method to perform certain single homocysteine test in August 1998 because it was quicker and more cost effective. Section 4.02 of the license agreement recognizes that LabCorp is entitled to use more cost-effective methods to perform assays for homocysteine. Dr. Wentz was correct in determining that LabCorp's performance of the single homocysteine test by the Abbott method is not covered by claim 13 of the '658 patent because the Court has specifically entered an order stating that LabCorp's performance of the single homocysteine test by the Abbott method is not covered by claim 13. After assaying a blood sample for homocysteine, LabCorp does not take any further action to correlate an elevated level, if any, with a vitamin deficiency but simply reports the result. In fact, over 80% of the results are not elevated. Although Dr. Wentz is not a patent lawyer, he was correct on this issue. On the other hand, plaintiffs CTI and Metabolite, who have been represented by patent attorneys, incorrectly accused LabCorp of directly infringing claim 13 of the '658 patent.

LabCorp has not induced or contributed to the infringement of any claim of the '658 patent because the single homocysteine tests have a substantial noninfringing use, including to screen and monitor patients for risk of heart disease. The American Heart Association has specifically recommended this use of the single homocysteine assays based on a discovery made by Dr. Kilmer McCully in 1969. CTI admitted this use of the assays in a 1999 press release.

Defendant contends that claims 13 and 18 are invalid and unenforceable for several reasons.

INSTRUCTION NO. 3

Each party in this case asserts that certain facts exist in support of its claim or its defense and each party must prove such facts by the required weight of evidence known as the burden of proof. Each party's burden of proof remains the same throughout the case, *i.e.*, it never changes.

In human affairs, and even in scientific matters, absolute certainty of facts is seldom possible. Thus, proof of facts to an absolute certainty is not required. To protect the interests of the parties and to foster certain public policy goals, the law imposes different burdens in different types of cases. For instance, in criminal cases the defendant's guilt has to be proven "beyond a reasonable doubt." In civil cases, like this one, lower standards or burdens of proof are used.

Generally speaking, the burden of proof in civil cases, like this one, is known as the "preponderance of evidence" standard. Sometimes the law imposes a heavier burden of proof known as the "clear and convincing" evidence standard because of other public policy considerations. I will tell you when to apply each burden of proof standard.

There will be two burden of proof standards by which you must weigh the evidence in this case. Plaintiff has the burden of establishing infringement of the claims of its patent by a preponderance of the evidence. Defendant has the burden of

establishing patent invalidity and/or unenforceability by the heavier clear and convincing evidence standard.

I will instruct you as to the standard by which you must weigh the evidence on each issue involved in this case. In determining whether any fact in issue has been proven under either standard, you should consider the testimony of all witnesses, regardless of who called them, and a exhibits, regardless of who offered them, including all reasonable inferences from the testimony and exhibits as seem justified in view of your experience and common sense.

A preponderance of the evidence means such evidence which, when considered and compared with that opposed to it, has more convincing force and produces in your minds a belief that what is sought to be proved is more likely true than not true. Put in a slightly different way, a party's burden to establish or prove a claim by a preponderance of the evidence means proof which produces in your minds the belief that the facts offered in support of the claims are more likely so than not so.

Clear and convincing evidence involves a greater degree of persuasion than that which will satisfy a preponderance of the evidence standard. The evidence must be highly probable and free from serious doubt. For purposes of evaluating evidence where a party has the burden of proof by clear and convincing evidence, that evidence must produce in your minds a firm belief or conviction as to the matter sought to be established. You must be convinced that the fact which that party seeks to prove is indeed true in order to meet the clear and convincing burden.

INSTRUCTION NO. 4

The evidence in the case consists of all the sworn testimony of all the witnesses, all exhibits which have been received in evidence, all facts which have been admitted or agreed to.

In deciding the facts, you must consider only the evidence received at trial. Evidence offered at the trial and rejected or stricken by the Court must not be considered by you. Statements, remarks, arguments, and objections by counsel and remarks of the Court not directed to you are not evidence.

You are to consider only the evidence in the case and the reasonable inferences from that evidence. An inference is a decision or conclusion which reason and common sense lead the jury to draw from other facts which have been proved.

INSTRUCTION NO. 5

Any finding of fact you make must be based on probabilities, not possibilities. You should not guess or speculate about a fact.

INSTRUCTION NO. 6

Evidence may be either direct or circumstantial. Circumstantial evidence is the proof of facts or circumstances from which the existence or nonexistence of other facts may reasonably be inferred. All other evidence is direct evidence. The law makes no distinction between the effect of direct evidence and circumstantial evidence.

INSTRUCTION NO. 7

The weight of evidence is not necessarily determined by the number of witnesses testifying to a particular fact.

INSTRUCTION NO. 8

The lawyers have highlighted certain parts of some exhibits. However, it is for you to determine the significance of the highlighted parts.

INSTRUCTION NO. 9

When a corporation is involved, of course, it may act only through natural persons as its agents or employees; and, in general, any agent or employee of a corporation may bind the corporation by his acts and declarations made while acting within the scope of his authority delegated to him by the corporation, or within the scope of his duties as an employee of the corporation.

INSTRUCTION NO. 10

You are the sole judges of the credibility of the witnesses and the weight to be given their testimony. You should take into consideration their means of knowledge; strength of memory and opportunities for observation; the reasonableness or unreasonableness of their testimony; the consistency or lack of consistency in their testimony; their motives; whether their testimony has been contradicted or supported by other evidence; their bias, prejudice or interest, if any; their manner or demeanor upon the witness stand; and all other facts and circumstances shown by the evidence which affect the credibility of the witnesses.

Based on these considerations, you may believe all, part or none of the testimony of a witness.

INSTRUCTION NO. 11

A witness qualified as an expert by education, training, or experience may state opinions. You should judge expert testimony just as you would judge any other testimony. You may accept it or reject it, in whole or in part. You should give the testimony the importance you think it deserves,

considering the witness's qualifications, the reasons for the opinions, and all of the other evidence in the case.

INSTRUCTION NO. 12

Certain testimony has been read into evidence or presented as videotape evidence from a deposition. A deposition is testimony taken under oath before the trial and preserved in writing. You are to consider that testimony as if it had been given by the witness from the witness stand.

INSTRUCTION NO. 13

Plaintiff Metabolite's first claim against defendant is for breach of the licensing agreement or contract. To establish their claim against the defendant, plaintiffs must prove that:

1. Metabolite did what the contract required Metabolite to do.

2. Defendant did not do what the contract required defendant to do. This is called a breach of the contract.

3. Defendant's breach, or failure to do what the contract required, caused a loss to plaintiffs.

If you find plaintiffs proved these three elements, then your verdict must be for plaintiffs on this claim. If you find that plaintiffs have not proved these elements, then your verdict must be for defendant on this claim.

INSTRUCTION NO. 14

A. Plaintiffs claim the following terms were part of the license agreement.

(1) LabCorp was required to pay plaintiffs a royalty of 27.5% of the billed amount on each homocysteine test and each methylmalonic acid test within 60 days after each calendar quarter.

(2) LabCorp was required to include with each royalty report to plaintiffs a certification by an officer certifying that the royalty report was accurate.

(3) LabCorp was prohibited from terminating the license agreement with respect to any particular homocysteine test unless the test was replaced by another test and LabCorp's actions in performing the other test did not infringe any valid and enforceable claim of the patent, either directly, contributorily or by inducement.

(4) LabCorp was required to give plaintiffs 60 days advance notice of any termination of the agreement with respect to any homocysteine or methylmalonic acid test.

B. Defendant claims the following terms were part of the license agreement.

"(1) LabCorp is only required to pay a royalty of 21.5% of net sales actually received on Licensed Assays to Metabolite and a royalty of 6% of net revenue billed after discounts and adjustments on Licensed Assays to Competitive Technologies. Payments are due within 60 days after each calendar quarter.

(2) LabCorp is entitled to perform the single homocysteine assay by the Abbott method which is not covered by the license agreement or the '658 patent without providing notice or terminating the agreement because LabCorp continues to use the licensed gas chromatography mass spectrometry method for assaying homocysteine in the panel test.

Plaintiffs have the burden to prove what the parties intended the contract to mean. The contract is to be interpreted so as to give effect to the parties' intentions. You cannot make for the parties a better contract than the parties made for themselves. It is the intent expressed or apparent in the writing that controls.

The interpretive principles which follow are not intended to be exhaustive, but they are intended to cover the most frequently utilized principles.

In deciding what the parties intended, you may consider the relations of the parties, the attendant circumstances and the result the parties sought to attain.

A supporting or less significant provision of the contract is not to be interpreted to conflict with an obvious, dominant or principal purpose of the contract.

You should carefully consider the wording that was used in the contract. The terms of a contract, generally, are to be understood in their plain ordinary sense. The contract is to be considered as a whole and its provisions are to be read together. The conduct of the parties, however, after they entered into the contract and before they discovered that they disagreed with one another, can be significant evidence of their agreed intent. It is up to you to decide what the conduct of the parties was, whether the conduct is reasonably related to the terms in question and whether it reveals what they intended by the contract.

A course of dealing is the manner by which parties to the contract have previously dealt with each other. Such a course of previous dealing, can, unless specifically rejected in the contract, fairly be regarding as establishing a basis for interpreting and giving meaning to the parties' intention as it relates to this contract.

If any contract words or terms have a technical meaning, or as used in a trade or by custom mean something different from their ordinary meaning, you shall give them their technical trade or custom meaning if (1) the contract was made in view of this technical meaning, trade or custom usage, and (2) the technical meaning or trade or custom usage was either generally used or was actually known to the parties.

If you have considered all of the evidence to ascertain the intentions of the parties and you are still unable to decide what the parties originally intended the disputed contract language to mean, then that language as it exists should be interpreted against the party to who wrote the contract. Although the general rule is that ambiguity in a contract provision should be resolved against the drafter, the ambiguous provision must be read sensibly and consistent with the expressed intent of the parties.

INSTRUCTION NO. 15

The second element of the breach of contract claim is that the contract was breached. Failure to perform a contract in accordance with its terms constitutes a breach of contract. It does not matter if the failure was purposeful or inadvertent.

A. Plaintiffs claim defendant breached the license agreement in the following manner:

(1) Defendant wrongfully terminated the license agreement with respect to the homocysteine-only test. This is because defendant's actions in performing that test constitute, but for the existence of the license agreement, infringement of the patent either directly, contributorily or by inducement.

(2) Defendant failed to comply with the provision of the License Agreement requiring 60 days advance notice to Metabolite of a termination with respect to any particular test.

B. Defendant denies this. Defendant contends:

(1) LabCorp did not terminate the License Agreement with respect to any Licensed Assay. LabCorp continues to perform homocysteine assays by gas chromotography/mass spectrometry, and pays plaintiffs royalties on those assays.

(2) LabCorp does not owe any royalties for the single homocysteine test performed by the Abbott method because it is not covered by the license agreement or the '658 patent.

INSTRUCTION NO. 16

A plaintiff - Metabolite in this case - who is awarded a verdict for breach of contract is entitled to compensatory damages for such losses as may fairly be considered to have arisen naturally from defendants' breach of contract. Alternatively, Metabolite may be entitled to such damages as may reasonably be supposed to have been contemplated by both parties, at the time they made the contract, as the probable result of the breach of such contract.

Compensatory damages for breach of contract are designed under the law to place the injured party in as good a monetary position as it would have enjoyed if the contract had been performed as promised.

INSTRUCTION NO. 17

Now, I will turn to the patent issues. I will be instructing you on issues where it will be necessary for you to determine what is a person of ordinary skill in the field of homocysteine and vitamins B_{12} and folate at the time the invention was made. This is called a person of ordinary skill in the art.

LabCorp contends that claims 13 and 18 of the '658 patent are invalid because the claimed invention was obvious to one of ordinary skill in the art at the time the invention was made. LabCorp bears the burden of proving this defense by clear and convincing evidence.

A person of ordinary skill in the art is presumed to be one who thinks along the line of conventional wisdom in the art. He or she is not one who undertakes to innovate, either by patient and expensive systematic research or by extraordinary insights.

The parties agree that the level of ordinary skill in the field of medicine relating to homocysteine was a person having a medical degree and experience in researching the amino acid, homocysteine, and its relationship to diseases.

When you decide the issue of obviousness, you must decide whether or not the invention would have been obvious to one having this ordinary level of skill in the field of science and medicine relating to homocysteine.

To be patentable an invention must not have been obvious to a person of ordinary skill in the pertinent art at the time the invention was made. The issue is not whether the claimed invention would have been obvious to you as a layman, to me as a judge, or to a genius in the art, but whether it would have been obvious to one of ordinary skill in the field of science and medicine of homocysteine at the time it was made.

You should conclude that the patent in suit is invalid even though not identically disclosed in a single prior art device of reference, only if LabCorp has established by clear and convincing evidence facts which show that the claimed invention as a whole would have been obvious to a person of ordinary skill in the field of science and medicine of homocysteine at the time the invention was made.

Before determining whether or not LabCorp has established obviousness of the claimed invention, you must determine the following factual matters, each of which must be established by clear and convincing evidence:

1. The scope and content of the prior art relied upon by LabCorp;

2. The difference or differences, if any, between each claim of the '658 patent and the prior art; and

3. The level of ordinary skill in the art at the time the invention of the '658 patent was made.

4. Commercial success; long-felt need; independent invention by others; failure by others; copying; acceptance of licenses.

Against this background of facts you will then make your conclusion whether or not the claimed subject matter would have been obvious to a person of ordinary skill in the art of medicine relating to the use of assays of homocysteine at the time the invention was made. When doing so, each claim must be considered in its entirety and separately from the other claims.

INSTRUCTION NO. 18

I will now instruct you as to the rules you are to follow in arriving at your decisions as to whether defendant has infringed claim 13 of the '658 patent owned by plaintiff Competitive Technologies by inducement and contributorily. The Court has held that LabCorp does not directly infringe claim 13. However, I have not determined, and leave for your determination whether LabCorp's performance of its homocysteine-only test constitutes contributory infringement or infringement by inducement of claim 13. You will be asked to answer specific questions in the verdict form about these decisions.

In determining infringement, you must consider the scope of the claims as I have interpreted them. Although you have heard discussions during the trial as to embodiments or examples in the '658 description, a claim is not necessarily limited to such embodiments or specific examples in the patent. The law does not require the impossible and does not require that the applicant describe in his specification every conceivable and possible future embodiment of his invention. The specification merely illustrates at least one embodiment of the invention and teaches a person of ordinary skill in the art how to make and use it. The scope of the patent grant is not limited to this embodiment, but is limited only by what is within the scope of the claims.

I will now read you claim 13 as construed by the Court.

Claim 13: A method for "determining the existence of" "a shortage of cobalamin or folate necessary to health" in warm-

blooded animals comprising the steps of 1) assaying a body fluid for a level of total homocysteine "raised above the normal range" and 2) to establish a mutual or reciprocal relationship between" a level of total homocysteine "raised above the normal range" in said body fluid with "a shortage of cobalamin or folate necessary to health." the latter step describes a discrete step in a sequential process.

LabCorp cannot avoid infringement by the mere fact that the accused homocysteine-only test may be more or less efficient or may include features or functions not found in the patent.

INSTRUCTION NO. 19

You will note that there is a part of plaintiffs claim which reads: ". . . comprising . . .". Such a word means that the claim is open-ended. This means that if you find that a method contains each and every one of the elements of any of the patent claims but, in addition, also contains additional steps, then acts in connection with its performance of its homocysteine-only test nevertheless infringes.

INSTRUCTION NO. 20

In this case, plaintiffs assert that defendant has contributorily or by inducement infringed claim 13 of the '658 patent. Infringement occurs if you find that the plaintiffs have proven by a preponderance of the evidence that others have performed the second step of claim 13 using assays done by defendant and that defendant has contributed to or induced that infringement by others. It is not necessary for the infringer to be made a party to a case against one who infringes by inducement or contributorily. I will later instruct you on contributory and inducing infringement.

Infringement does not depend on bad faith. A person can infringe a patent even though in good faith it believes that what it is doing is not an infringement of the patent. It may also infringe even though in good faith it believes that what it is doing is not an infringement of any patent.

INSTRUCTION NO. 21

To show infringement of claim 13 by inducement, plaintiffs must prove by a preponderance of the evidence that someone has directly infringed claim 13. If there is no direct infringement of claim 13 by anyone, defendant has not induced infringement. If you find that someone has directly infringed claim 13, it is not necessary to show that defendant LabCorp itself has directly infringed, if plaintiffs prove by a preponderance of the evidence that LabCorp actively and knowingly aided and abetted that direct infringement. Plaintiffs must show that LabCorp knew or should have known that its actions would induce actual infringement. LabCorp cannot be liable for inducing infringement if it had no reason to be aware of the existence of the patent.

If you find that someone has directly infringed claim 13 and that LabCorp knew or should have known that its actions would induce direct infringement, you may find that LabCorp induced another to infringe claim 13 if it provided instructions and directions to perform the infringing act through labels, advertising or other sales methods. You may find that LabCorp induced infringement even if there is an express warning against the infringement, if the material containing the warning nonetheless invites the infringing activities under the circumstances. You may find that LabCorp induced infringement by supplying the components that are used in an infringing method or apparatus with the knowledge and intent that its customer would directly infringe by using the components to make, use or sell the patented invention.

INSTRUCTION NO. 22

Plaintiffs assert that defendant is liable for contributory infringement of claim 13. Plaintiffs has the burden to prove contributory infringement by a preponderance of the evidence. To establish contributory infringement by defendant, plaintiffs must first show that someone directly infringed the '658 patent; however, plaintiffs do not need to prove that

defendant itself directly infringed. If there is no direct infringement by anyone, there can be no contributory infringement.

If you find someone has directly infringed the patent, then contributory infringement exists if plaintiffs prove that:

(1) LabCorp sold or supplied;

(2) a material component of the patented invention that is not a staple article of commerce capable of substantial noninfringing use;

(3) with knowledge that the component was especially made or adapted for use in an infringing method.

A "staple article of commerce capable of substantial noninfringing use" is something that has uses other than the patented method and that those other uses are not occasional, farfetched, impractical, experimental or hypothetical.

INSTRUCTION NO. 23

Now I will instruct you about certain defenses defendant has raised to plaintiffs' allegations of patent infringement.

Under the law, plaintiff's patent is presumed valid. The presumption of validity goes to the validity of plaintiff's patent in relation to the patent statute as a whole, no matter on what grounds defendant seeks to invalidate plaintiff's '658 patent.

Each claim of plaintiff's patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of what you find as to the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon what you find to be an invalid claim.

The burden upon defendant, who challenges the validity of the '658 patent, is to introduce evidence of facts establishing

invalidity (thus overcoming the presumption of validity). That evidence, if defendant is to prevail, must be clear and convincing. That is a heavier burden than preponderance of the evidence.

Because you have heard that defendant has introduced prior art not considered by the examiner, a situation which is common in a patent trial, this does not "weaken" or otherwise affect the presumption of validity.

In the end, you must decide whether all the evidence introduced by both sides, whether considered by the examiner or not, establishes that defendant has carried its burden so as to have persuaded you by clear and convincing evidence that the '658 patent can no longer be accepted as valid.

INSTRUCTION NO. 24

If you find by a preponderance of the evidence that LabCorp was licensed under the '658 patent and that the license has not been terminated with respect to the tests at issue, then you must find that LabCorp has not infringed the '658 patent.

INSTRUCTION NO. 25

You have heard the term "prior art" used by the parties in this trial. These terms are used in connection with facts or events which by law prevent an applicant from obtaining a patent or, if a patent has been issued, renders such a patent invalid. The law provides that a patent cannot be obtained if the invention was:

1. known or used by others in this country before the date of invention by the inventors of the patent; or

2. patented or described in a printed publication in this or a foreign country more than one year prior to the date of the application which resulted in the patent.

I will now review these items with you separately with regard to the evidence you have heard in this case.

INSTRUCTION NO. 26

In determining whether the invention of the patent in suit would have been obvious to a person of ordinary skill in the art, you must presume that person would have known about all of the relevant prior art. A combination of prior art cannot render an invention obvious unless every one of the elements of the claimed invention is disclosed in at least one of those items of prior art. In examining the prior publications, you should take into account not only what they expressly disclose, but also anything that inherently occurred as a result of practicing what was expressly disclosed in that prior art.

If you find that a combination of items of the prior art showed each of the elements of the claims in suit, you must determine whether or not it would then have been obvious to a person of ordinary skill in the art of medicine relating to homocysteine to combine or coordinate these elements in the same manner as the claims of the '658 patent. You must not use hindsight in answering this question. In other words, it is wrong to use the '658 patent as a guide through the prior art references, combining the right references in the right way so as to achieve the result of the claims of the '658 patent. Rather, you must determine whether or not, at the time the invention was made, the invention of the '658 patent would have been obvious to one of ordinary skill in the art having knowledge of all the prior art.

If you conclude that the prior art discloses all the elements of the claimed invention, but those elements are in separate prior art references, you must then consider whether or not it would have been obvious to combine the elements. To answer this question "yes," you must determine that there was some suggestion in the prior art to combine the elements. The suggestion can be expressly stated in a particular reference or it can be within the knowledge that was generally available to one of ordinary skill in the art of medicine relating to homocysteine.

INSTRUCTION NO. 27

In deciding whether the prior art suggests the method recited in the claims of the '658 patent, you are instructed that if the prior art merely discloses numerous possible combinations but gives no direction as to which of those of many choices is likely to be successful, this does not constitute a suggestion of the claimed method. Similarly, if the prior art merely discloses that it would be obvious to explore a new technology or general approach that seemed to be a promising field of experimentation, this would not constitute a suggestion of the claimed method.

On the other hand, for the prior art to "suggest" the claimed invention, it is not necessary that one of ordinary skill in the medical art, looking at the prior art, could predict with certainty that the claimed invention would be successful. Rather, it is sufficient that a person of ordinary skill in the medical art, looking at the prior art, would have a reasonable expectation that the claimed invention would achieve the desired result.

INSTRUCTION NO. 28

Before deciding the issue of obviousness, you must consider certain factors. Some weigh in favor of finding that the invention was obvious; some do not.

One of the factors you should consider is whether or not plaintiff has shown any commercial success of products covered by the patent in suit due to the merits of the claimed invention. To prove this, plaintiff would have to satisfy you that there is a causal connection between the evidence showing the commercial success and the claimed invention. For example, if you conclude that commercial success is due to advertising, promotion, salesmanship or the like, or to features of the product other than those claimed in the patent in suit, rather than to the claimed invention, then it is not established that commercial success has a relation to the invention itself. If, however, you were to find that the

invention of the '658 patent achieved commercial success and that the merits of the invention caused the commercial success this would tend to indicate that the invention was not obvious.

You should also consider whether or not the claimed invention was invented independently by other persons, either before it was invented by the inventor of the patent in suit or at about the same time. Just as the failure of others to make the invention may be evidence that an invention was not obvious, independent making of the invention by persons other than the inventor about the same time may be evidence that the invention was obvious.

INSTRUCTION NO. 29

Another factor you should consider is whether or not plaintiff has shown that others had tried, but failed to solve the problem solved by the invention of the '658 patent. To prove this plaintiff must show that others had tried and failed and that it was the merits of the claimed invention that allowed the inventors of the '658 patent to succeed where others had failed. For example, if advances in unrelated technology allowed the inventor of the '658 patent to succeed where others had failed, then plaintiff would not have carried his burden of proof on this issue. If, however, you were to find that the merits of the invention allowed the inventor to succeed where others had failed, this would tend to indicate that the invention was not obvious.

Another factor you should consider is whether or not plaintiff has shown copying by others of the invention claimed in the '658 patent. If you were to find that others copied the invention because of its merits this would tend to indicate that the invention was not obvious.

Another factor you should consider is whether or not plaintiff has shown unexpected superior results achieved by the invention claimed in the '658 patent. To prove this plaintiff must show that it was the claimed invention that

caused the unexpected results. For example, if there were not unexpected superior results or the unexpected results were due to a feature unrelated to the claimed invention, then plaintiff would not have carried its burden of proof on this issue. If, however, you were to find that there were unexpected superior results which were related to the claim invention, this would tend to indicate that the invention was not obvious.

Another factor you should consider is whether or not plaintiff has shown that others have accepted licenses under the '658 patent. To prove this plaintiff must show that others agreed to licenses because of the merits of the claimed invention. For example, if the others accepted licenses due to factors such as the cost of litigation, or the low cost of the license, then it has not been established that the acceptance of licenses was due to the merits of the invention. itself. If, however, you were to find that others took licenses as a result of the merits of the claimed invention, this would tend to indicate that the invention was not obvious.

INSTRUCTION NO. 30

One of the requirements for a valid patent is that the invention defined in the claims must be new. This is known as the requirement of novelty. Something that shows that an invention was not new or novel is called an anticipation. There are several categories of events, all defined by the patent laws, that can anticipate and invalidate a patent. In this case, LabCorp contends that the claim 13 is of the '658 patent is anticipated because the invention of claim 13 of the '658 patent was described in the Refsum et al. article published by "Clinical Chemistry" in Vol. 31, no. 4 (1985) which Applicants acknowledged was prior art.

I will now instruct you as to the rules of law that you must follow in deciding whether or not the claim 13 of the '658 patent was anticipated.

First, LabCorp has the burden of proving anticipation by clear and convincing evidence.

Second, a publication anticipates a claim if it discloses the claimed invention sufficiently that a person of ordinary skill in the art could take its teachings together with his own knowledge of the art and be in possession of the claimed invention. To establish that anticipation exists, LabCorp must show that each of the elements recited in the claim was disclosed in the particular item claimed to be an anticipation. If every element of the claimed invention is shown to be present in the prior publication, the patent claim is anticipated.

Third, there is no anticipation unless every one of the elements of the claimed invention is found in a single prior publication. You may not combine two or more items of prior art to make out an anticipation. You should, however, take into consideration not only what is expressly disclosed or embodied in the particular item of prior publication but also what inherently occurred as a natural result of its practice. A party claiming inherency must prove it by clear and convincing evidence. It must show that the publication always inherently produces a process meeting all of the claim limitations. In determining whether or not every one of the elements of the claimed invention is found in the prior publication you should take into account what a person of ordinary skill in the art would have understood from his or her examination of the particular publication.

You must keep these requirements in mind and apply them to each kind of anticipation you consider in this case. There are additional requirements that apply to the particular categories of anticipation that LabCorp contends apply in this case. I will now instruct you about those.

INSTRUCTION NO. 31

The requirements of patentability require that the specification conclude with one or more claims that particularly

pointing out and distinctly claim the subject matter which the Applicant regards as his invention. Each claim must be considered separately.

If you find by clear and convincing evidence that claim 13 or claim 18 does not particularly point out and distinctly claim the invention, then you may find the claim is invalid for indefiniteness.

INSTRUCTION NO. 32

LabCorp contends that the Applicants (CTI and Allen) engaged in inequitable conduct before the United States Patent and Trademark Office. The question of whether Applicants engaged in inequitable conduct is a question for me to decide. However, I will decide that question based upon whether you find the following facts have been proved by clear and convincing evidence:

1. The Applicants, CTI or Allen, made a misrepresentation to the Patent and Trademark Office;

2. That any such misrepresentation was material; and

3. The degree to which you find that the Applicants acted with intent.

Applicants have a duty of honesty and candor when dealing with the patent office which precludes them making intentional, material misrepresentations. Misrepresentations can be in the form of either a false statement of a material fact or the omission of a material fact from a statement that was made. A fact is material when there is a substantial likelihood that a reasonable patent examiner would consider it important in deciding whether to allow the application as a patent.

The question of intent may be established by circumstantial evidence, based upon a person's outward manifestations, the person's words, conduct, acts, and all the surrounding circumstances disclosed by the evidence together with the

rational and logical inferences that may be drawn from them. If you find that CTI or Allen knowingly submitted a false or misleading statement that was material to the consideration of the patent application, you may, but are not required to, conclude that the statement was part of a deliberate scheme to deceive the Patent and Trademark Office.

Based on your findings of whether the misrepresentation was made, its materiality, and the intent of CTI or Allen, I will make the determination of whether CTI or Allen engaged in inequitable conduct.

INSTRUCTION NO. 33

Under the U.S. patent laws, a patent must disclose sufficient information to enable those skilled in the art to make and use the claimed invention. This requirement is known as the enablement requirement.

The defendant in this case has asserted that the plaintiff's patent is invalid for failure to satisfy the enablement requirement. As with assertions of patent invalidity on other grounds, the defendant bears the burden of establishing nonenablement by clear and convincing evidence.

To determine whether a patent is enabling, one must look to the time the application for that patent was filed. A patent is enabling if its disclosure is sufficient to enable a person of ordinary skill in the art to make and use the claimed invention. A patent need not disclose what is well known in the art.

A patent is enabling even if some experimentation would be required to achieve the claimed invention, so long as that amount of experimentation is routine and would not be considered undue by those skilled in the art. Factors to be considered in determining whether a disclosure would require undue experimentation include: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the patent; (3) the presence or absence of working examples in the patent; (4) the nature of the

invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability of the art; and (8) the breadth of the claims.

INSTRUCTION NO. 34

I will now instruct you on the law you must follow in determining patent infringement damages, if any.

The patent law specifically provides that the amount of damages that defendant must pay plaintiff for infringing plaintiff CTI's patent may not be less than a reasonable royalty for the use that defendant made of plaintiff's invention.

INSTRUCTION NO. 35

A royalty is a payment made to the owner of a patent by a non-owner in exchange for rights to make, use or sell the claimed invention. A reasonable royalty is the royalty that would have resulted from a hypothetical negotiation between plaintiff and a company in the position of defendant taking place at the time that the infringement began. You should also assume that both parties to that negotiation understood the patent to be valid and infringed and that the licensee would respect the patent.

INSTRUCTION NO. 36

In determining the value of a reasonable royalty, you may consider evidence on any of the following factors.

1. Any royalties received by plaintiff for the licensing of the patent in suit, proving or tending to prove an established royalty.

2. The rates paid by defendant to license other patents comparable to the '658 patent.

3. Plaintiff's established policy and marketing program to maintain his right to exclude others from using the patented invention by not licensing others to use the invention, or by

granting licenses under special conditions designed to preserve that exclusivity.

4. The commercial relationship between the licensor and the licensee, such as whether or not they are competitors in the same territory in the same line of business.

5. The effect of selling the patented product in promoting sales of other products of the licensee; the editing value of the invention to the licensor as a generator of sales of his non-patented items; and the extent of such collateral sales.

6. The duration of the patent.

7. The established profitability of the product made under the patent; its commercial success; and its current popularity.

8. The utility and advantages of the patented invention over the old modes or devices, if any, that had been used for achieving similar results.

9. The nature of the patented invention; the character of the commercial embodiment of it as owned and produced by the licensor; and the benefits to those who have used the invention.

10. The extent to which the accused infringer has made use of the invention; and any evidence that shows the value of that use.

11. The portion of the profit or of the selling price that may be customary in the particular business or in comparable businesses to allow for the use of the invention or analogous inventions.

12. The portion of the profit that arises from the patented invention itself as opposed to profit arising from features unrelated to the patented invention, such as the manufacturing process, business risks, or significant features or improvements added by the accused infringer.

INSTRUCTION NO. 37

Although the relevant date for the hypothetical reasonable royalty negotiation is the date that the infringement began, you may consider in your determination of reasonable royalty damages any actual profits by the defendant after that time and any commercial success of the patented invention in the form of sales of the patented or infringing products after that time. You may only consider this information, however, if it was foreseeable at the time that the infringement began.

INSTRUCTION NO. 38

You must not award plaintiff CTI more than the amount of damages adequate to compensate plaintiff CTI for defendant's infringement. You must not include any additional amount for the purpose of punishing defendant or setting an example.

In determining damages, you must not consider plaintiff's claims of willfulness, or take into account any evidence relating to those claims. The consideration of willfulness, if any, is entirely separate from the question of any damages you are asked to determine.

You should not increase damages because you find willfulness, or decrease damages because you do not find willfulness. In addition, you should not include any amount in your damages award for interest, attorney fees, or other expenses.

INSTRUCTION NO. 39

The patent owner has the burden of proving each element of its damages by a preponderance of the evidence.

INSTRUCTION NO. 40

You are instructed that you should begin calculating patent infringement damages as of the date that the infringement began on August 1, 1998.

INSTRUCTION NO. 41

You are instructed that where a potential infringer has actual notice of another's patent rights, he has an affirmative duty of due care not to infringe. Thus if you find by a preponderance of the evidence that LabCorp infringed the patent, then you must further determine if this infringement was willful. Willfulness must be proven by clear and convincing evidence showing that:

A. LabCorp had actual knowledge of the patent, and

B. LabCorp had no reasonable basis for believing that (a) LabCorp did not infringe the patent or (b) that the patent was invalid.

In making the determination as to willfulness, you must consider the totality of the circumstances. The totality of the circumstances comprises a number of factors, which include, but are not limited to whether the defendant intentionally copied the product covered by the patent, whether the defendant exercised due case to avoid infringing the patent, whether the defendant relied on competent legal advice, and the defendant's behavior as a party to the litigation.

INSTRUCTION NO. 42

You may not include damages that are speculative, only possible, or that are based on guesswork. Difficulty or uncertainty in determining the precise amount of any damages does not prevent you from deciding an amount. You should use your best judgment based on the evidence.

INSTRUCTION NO. 43

The fact that I have instructed you on the proper measure of damages should not be considered as any suggestion on which party is entitled to your verdict in this case. Instructions on the measure of damages are given for your guidance, in the event you find in favor of the plaintiff from a preponderance of the evidence in the case in accordance with the other instructions

INSTRUCTION NO. 44

These instructions contain the law that you must use in deciding this case. No single instruction states all the applicable law. All the instructions must be read and considered together.

You must not be concerned with the wisdom of any rule of law. Regardless of any opinion you may have as to what the law should be, it would be a violation of your sworn duty to base a verdict upon any other view of the law than that given in the instructions of the Court.

I do not, by these instructions, express any opinions as to what has or has not been proved in the case, or to what are or are not the facts of the case.

INSTRUCTION NO. 45

The Marshal will now escort you to the jury room. After you get to the jury room you shall select one of your members to be the foreperson of the jury. That persons will be in charge of your discussions. You must all agree on your verdict, and the foreperson must sign and date the original form of whatever verdict you reach.

(Read Verdict)

Please notify the Court when you have reached a verdict, but do not tell anyone what your verdict is. You shall keep the verdict forms, these instructions and the exhibits until I give you further instructions.

INSTRUCTION NO. 46

Once you begin your deliberations, if you have a question about the evidence in this case or about the instructions or verdict forms that you have been given, your Foreperson should write the question on a piece of paper, sign it and give it to the Marshal who will bring it to me.

I will then confer with the attorneys as to the appropriate way to answer your question. However there may be some questions that, under the law, I am not permitted to answer. If it is improper for me to answer the question, I will tell you that. Please do not speculate about what the answer to your question might be or why I am not able to answer a particular question.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLORADO

Civil Action No. 99-Z-870

METABOLITE LABORATORIES, INC.
a Colorado corporation, and
COMPETITIVE TECHNOLOGIES, INC.,
a Delaware corporation,

Plaintiffs,

vs.

LABORATORY CORPORATION OF AMERICA
HOLDINGS d/b/a LabCorp, a Delaware corporation,

Defendant.

Special Verdict Form
[Filed November 20, 2001]

We, the jury, upon our oath, unanimously answer the questions in this Special Verdict Form as follows:

1. Do you find, by a preponderance of the evidence, that Defendant LabCorp is licensed under the '658 patent and that license has not been terminated in whole or in part?

_____ Yes __X__ No

IF YOU ANSWERED "YES" TO QUESTION NO. 1, THEN ANSWER QUESTION NO. 2. IF YOU ANSWERED "NO" TO QUESTION NO. 1, THEN GO TO QUESTION NO. 5 AND 6.

2. Do you find, by a preponderance of the evidence, that LabCorp breached the License Agreement with Plaintiff Metabolite by failing to pay Plaintiffs royalties on the Abbott homocysteine test?

_____ Yes _____ No

IF YOU ANSWERED "YES" TO QUESTION NO. 2, ANSWER QUESTION NOS. 3 AND 4. IF YOU ANSWERED "NO" TO QUESTION NO. 2, DO NOT ANSWER QUESTION NOS. 3, 4, 5, 6, 7, 8 and 9, ANSWER QUESTION NOS. 10 AND 11.

3. State the amount of royalties due, if any, to Plaintiff Metabolite, under the License Agreement, Section 2.02, which provides for a royalty of 21.5%. (Exhibit AC)

$_____

4. State the amount of royalties due, if any, to Plaintiff CTI under the License Agreement, Section 2.03, which provides for a royalty of 6%. (Exhibit AC)

$_____

UPON COMPLETION OF QUESTION NOS. 3 AND 4, DO NOT ANSWER QUESTIONS NOS. 5, 6, 7, 8 AND 9 BUT ANSWER QUESTION NOS. 10 AND 11.

5. Do you find, by a preponderance of the evidence, that LabCorp breached its license agreement by terminating it with respect to its performance of the Abbott test?

__X__ Yes _____ No

IF YOU ANSWERED "YES" TO QUESTION NO. 5, THEN ANSWER THE REST OF THE QUESTIONS. IF YOU ANSWERED "NO" TO QUESTION NO 5, THEN GO TO QUESTION NO 10 AND 11.

6. State the damages, if any, to plaintiff Metabolite for the breach of contract.

$3,652,724.61

7. Do you find, by a preponderance of the evidence, that Defendant LabCorp has contributed to or induced infringement of claim 13 of the '658 patent?

Induced infringement of Claim 13:

__X__ Yes _____ No

Contributed to infringement of Claim 13:

__X__ Yes _____ No

IF YOU ANSWERED "YES" TO ANY PART OF QUESTION NO. 7, COMPLETE QUESTION NOS. 8 AND 9. IF YOU ANSWERED "NO" TO BOTH PARTS OF QUESTION NO. 7, THEN DO NOT ANSWER QUESTION NOS. 8 AND 9 AND ANSWER QUESTION NOS. 10 AND 11.

8. State the amount of damages, if any, to Plaintiff CTI caused by Defendant LabCorp's infringement by inducement or by contributory infringement.

$1,019,365.01

9. Do you find, by clear and convincing evidence, that LabCorp has willfully infringed claim 13 of the '658 patent?

__X__ Yes _____ No

YOU MUST ANSWER QUESTION NOS. 10 and 11.

10. Do you find, by clear and convincing evidence, that claims 13 or 18 of the '658 patent are invalid?

_____ Yes __X__ No

IF YOU ANSWERED "YES" STATE WHICH CLAIMS ARE INVALID:

Invalid for Nonenablement:	Claim 13 _____
	Claim 18_____
Invalid for Insufficient Written Description:	Claim 13_____
	Claim 18_____
Invalid for Indefiniteness:	Claim 13_____
	Claim 18_____
Invalid for Obviousness:	Claim 13_____
	Claim 18_____
Invalid for Anticipation:	Claim 13_____

11. Do you find, by clear and convincing evidence, that:

(a) CTI or one of the inventors of the '658 patent withheld information or misrepresented information that was material to the patent examiner's examination of the claims of the patent?

_____ Yes __X__ No

(b) CTI or one of the inventors of the '658 patent withheld material information or made material misrepresentations with the intent to deceive the patent examiner in allowing the '658 patent to issue?

_____ Yes __X__ No

After answering the appropriate questions, the foreperson should date and sign the verdict form.

Dated: November 20, 2001

/s/ John MacKay
FOREPERSON

[Filed Dec. 3, 2001]

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLORADO

Civil Action No. 99-Z-870

METABOLITE LABORATORIES, INC.,
a Colorado corporation, and
COMPETITIVE TECHNOLOGIES, INC.,
a Delaware corporation,

Plaintiffs,

v.

LABORATORY CORPORATION OF AMERICA
HOLDINGS d/b/a LABCORP,
a Delaware corporation,

Defendant.

JUDGMENT

This matter came on for trial before the Court and a jury of eight beginning on November 5, 2001, the Honorable Zita L. Weinshienk, United States District Judge, presiding.

At the conclusion of all of the evidence, the jury returned its Special Verdict Form on November 20, 2001, which is incorporated herein by reference as if fully set forth. Accordingly, it is

ORDERED that a judgment is entered in favor of the plaintiffs Metabolite Laboratories, Inc. and Competitive Technologies and against defendant Laboratory Corporation of America Holdings. It is

FURTHER ORDERED that the damages to be awarded to plaintiff Metabolite for defendant LabCorp's breach of contract are $3,652,724.61. It is

FURTHER ORDERED that the damages to be awarded to plaintiff Competitive Technologies, Inc., due to defendant LabCorp's infringement by inducement or by contributory infringement are $1,019,365.01. It is

FURTHER ORDERED that post-judgment interest shall accrue at the legal rate of 2.23% per annum from the date of entry of judgment.

DATED, at Denver, Colorado, this 3 day of December, 2001.

BY THE COURT:

/s/ Zita L. Weinshienk
ZITA L. WEINSHIENK, Senior Judge
United States District Court

[Filed Nov. 20, 2002]

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLORADO

Civil Action No. 99-Z-870

METABOLITE LABORATORIES, INC.,
a Colorado corporation, and
COMPETITIVE TECHNOLOGIES, INC.,
a Delaware corporation,

Plaintiffs,

v.

LABORATORY CORPORATION OF AMERICA
HOLDINGS d/b/a LABCORP,
a Delaware corporation,

Defendant.

AMENDED JUDGMENT

This matter came on for trial before the Court and a jury of eight beginning on November 5, 2001, the Honorable Zita L. Weinshienk, United States District Judge, presiding.

At the conclusion of all of the evidence, the jury returned its Special Verdict Form on November 20, 2001, which is incorporated herein by reference as if fully set forth. Accordingly, it is

ORDERED that a judgment is entered in favor of the Plaintiffs Metabolite Laboratories, Inc. and Competitive Technologies and against Defendant Laboratory Corporation of America Holdings. It is

FURTHER ORDERED that damages are awarded to Plaintiff Metabolite for Defendant LabCorp's breach of contract in the amount of $3,652,724.61. It is

FURTHER ORDERED that damages are awarded to Plaintiff Competitive Technologies, Inc., due to Defendant LabCorp's infringement by inducement or by contributory infringement in the amount of $1,019,365.01. It is

FURTHER ORDERED that enhanced damages are awarded to Plaintiff Competitive Technologies, Inc. in the amount of $1,019,365.01. It is

FURTHER ORDERED that Plaintiff Metabolite Laboratories, Inc. is awarded $473,946.97 in prejudgment interest. It is

FURTHER ORDERED that Plaintiff Competitive Technologies, Inc. is awarded $132,264.27 in prejudgment interest. It is

FURTHER ORDERED that post-judgment interest shall accrue at the legal rate of 2.23% per annum from the date of entry of judgment.

DATED at Denver, Colorado, this 19 day of November, 2002.

BY THE COURT:

/s/ Zita L. Weinshienk
ZITA L. WEINSHIENK, Senior Judge
United States District Court

Supreme Court of the United States

No. 04-607

LABORATORY CORPORATION OF AMERICA HOLDINGS, dba LabCorp,

Petitioner,

v.

METABOLITE LABORATORIES, INC., et al.,

Respondents

Order of October 31, 2005

Petition for writ of certiorari to the United States Court of Appeals for the Federal Circuit granted limited to Question 3 presented by the petition.

Supreme Court of the United States

No. 04-607

LABORATORY CORPORATION OF AMERICA HOLDINGS, dba LabCorp,

Petitioner,

v.

METABOLITE LABORATORIES, INC., et al.,

Respondents

Order of November 2, 2005

Having been advised by THE CHIEF JUSTICE that he now realizes that he should have recused himself from participation in this case, and does now recuse himself, the Court vacates its order of Monday, October 31, 2005. The Court has reconsidered the petition for certiorari, which is granted but limited to question three as presented in the petition. THE CHIEF JUSTICE has not participated in the vote to withdraw the order of October 31, 2005, or in the instant reconsideration of the petition for certiorari.

of the patent." *Manual of Patent Examining Procedure* § 2173.02. Petitioner's indefiniteness challenge is that "[t]he claim as construed says *nothing* at all about what it means to actively 'correlate' a test result." Pet. Br. 39. This argument cannot be reconciled with the record or petitioner's own litigating position in the lower courts.

In the district court, *petitioner* proposed that "correlating" means to "establish a mutual or reciprocal relationship." Pet. App. 7a-8a. The district court adopted that proposed construction and then petitioner stipulated to it in a jury instruction:

> A method for determining the existence of a shortage of cobalamin or folate necessary to health in warm-blooded animals comprising the steps of 1) assaying a body fluid for a level of total homocysteine raised above the normal range and 2) establish[ing] a mutual or reciprocal relationship between a level of total homocysteine raised above the normal range in said body fluid with a shortage of cobalamin or folate necessary to health[,] the latter step describ[ing] a discrete step in a sequential process.

J.A. 376-377 (internal quotations omitted). The Federal Circuit agreed that establishing a mutual or reciprocal relationship was a sufficiently definite description. Pet. App. 16a; *see also* U.S. Br. 14 ("[C]laim 13 satisfies the definiteness requirement because it marks the boundaries of the patent claim with precision. . . . Although [the claim] language is undeniably sweeping, it is not unclear.").

Petitioner presented no evidence at trial to support its current assertion that the correlating step is unclear. To the contrary, its own medical expert, its own Discipline Director, and its own Laboratory Director all testified that the step was quite clear to them. J.A. 154, 150-151, 162-164, 112-113. In its jury instruction contentions, petitioner failed to assert that

the correlating step was unclear. J.A. 365-366, 385-388. In its opening statement and closing argument, petitioner never asserted that the correlating step was unclear. Trial Tr. 131-141, 1772-1798.

Petitioner itself has published extensive materials explaining the mutual and reciprocal relationship between total homocysteine and cobalamin and folate deficiencies. *See* J.A. 189-195, 255-256, 257-258, 259-261. Petitioner's literature acknowledges that the Inventors discovered "the clinical correlations and analytical methodology," and in particular that they had patented "methods for detecting and distinguishing cobalamin and folic acid deficiency." J.A. 196. Until it stopped paying royalties, petitioner never questioned the validity of the '658 patent on any grounds.

Now, as if the burden were on respondents to disprove petitioner's bald contention that *its own* construction of "correlating" is unclear, petitioner protests that "nothing . . . tells a practitioner how to actively 'establish' a 'relationship' between a particular test result and a vitamin deficiency." Pet. Br. 39. This assertion cannot be reconciled with the specification itself, which teaches that "[h]omocysteine levels above [the normal] ranges are indicative of cobalamin and/or folate deficiency; the higher the level, the stronger the indication." S.A. 14; *see also* S.A. 11. The patent goes on to quantify the total homocysteine ranges in the sample populations and to describe in detail the procedures by which the Inventors established the mutual and reciprocal relationship between total homocysteine and vitamin deficiency.[7] As the Federal Cir-

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[7] Example I, Example VI, and Example VII all describe the Inventors' extensive patient studies, in which they established that total homocysteine was "diagnostically useful" in evaluating vitamin deficiencies and "more sensitive" than previous tests. S.A. 14-15, 27-29. These examples parallel the papers authored by the Inventors and published—after peer review—in prestigious medical journals. C.A. App. 8885-8895, 8644-8652, 8862-8871.

cuit explained, "the record shows repeatedly that the correlating step is well within the knowledge of one of skill in this art." Pet. App. 18a. Petitioner has not demonstrated any error in that factual determination.

B. The Specification Contains A Sufficient Written Description And Enables One Skilled In The Art To Practice The Invention

The jury and lower courts correctly concluded that the specification also contains a sufficient written description of the invention and enables a person skilled in the art to make and use the invention. J.A. 396-397; Pet. App. 34a-35a, 17a-18a.

1. The purpose of the written description requirement is to "convey to a person of skill in the art that the patentee had possession of the claimed invention at the time of the application, i.e., that the patentee invented what is claimed." *LizardTech, Inc.* v. *Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed Cir. 2005); *see Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirements*, 66 Fed. Reg. 1099, 1104 (Jan. 5, 2001). As with its definiteness challenge, petitioner's sole challenge to the written description of the invention is that "nothing in the specification says exactly what [the correlating step] includes or how to do it." Pet. Br. 41. To the contrary, the specification explains that "[i]t has been discovered that elevated levels of homocysteine in body tissue correlate with decreased levels of cobalamin and/or folic acid in said body tissue." S.A. 12. The patent recites several prior-art methods of assaying for total homocysteine, but notes that "[t]he procedure has never been used to monitor homocysteine to detect or measure cobalamin or folic acid deficiency." *Ibid.*

The patent clearly describes how the Inventors practiced the correlating step en route to inventing the diagnostic

method of claim 13. *See* note 7 and accompanying text, *supra*; U.S. Br. 9 ("the patent specification easily satisfies the . . . written description requirement[] by . . . demonstrating that the applicants had in fact performed [the claimed method]"). Moreover, the Federal Circuit explained that "the PTO read the specification to include [the correlating] feature," and "the record reflects that [petitioner's] own expert and employees understood the meaning of 'correlating.'" Pet. App. 17a. Petitioner has not challenged either of these factual determinations as clearly erroneous—indeed, petitioner does not take issue with any aspect of the lower courts' rejection of its written description defense. Because the written description issue is "primarily factual" (*Union Oil Co.* v. *Atlantic Richfield Co.*, 208 F.3d 989, 1005 (Fed. Cir. 2000); *see* U.S. Br. 11), and "[t]he record is replete with evidentiary support" that one skilled in the art would "underst[and] from the specification that the '658 patent inventors possessed the 'correlating' step" (Pet. App. 17a), petitioner's written description argument fails.

2. The specification also easily meets the enablement requirement, which "is satisfied when one skilled in the art, after reading the specification, could practice the claimed invention without undue experimentation." *AK Steel Corp.* v. *Sollac & Ugine*, 344 F.3d 1234, 1244 (Fed. Cir. 2003).

Petitioner's sole enablement challenge is that "nothing in the specification informs a skilled artisan what [the correlating step] is." Pet. Br. 41. This is wrong for the reasons just discussed: Since the specification describes in detail how the Inventors practiced the correlating step, it would enable one skilled in the art to replicate (or build upon) their research.

In fact, the specification describes in great detail the manner in which to conduct assays and correlations. For example, the specification describes "several different known assays suitable for use in determining levels of homocysteine in urine or blood," S.A. 12, as well as a new assay method

claimed in the '658 patent, S.A. 12-14. As the Federal Circuit explained, "the record shows repeatedly that the correlating step is well within the knowledge of one of skill in this art." Pet. App. 18a; *see* U.S. Br. 9 ("Especially from the perspective of such a person, the patent specification easily satisfies the enablement . . . requirement[] by explaining precisely how to perform the claimed method"). Petitioner has not even challenged this factual conclusion.

II. Petitioner's Contention That Claim 13 Does Not Recite Patentable Subject Matter Is Not Properly Presented, And In Any Event Is Meritless

Section 101 of the Patent Act provides that "*[w]hoever invents or discovers any new and useful process*, machine, manufacture, or composition of matter, *may obtain a patent therefor*, subject to the conditions and requirements of this title." 35 U.S.C. § 101 (emphases added). As this Court has recognized (*Diamond* v. *Chakrabarty*, 447 U.S. 303, 315 (1980)), Section 101 is the congressional implementation of the constitutional authority to "promote the Progress of Science and useful Arts, by securing for limited Times to . . . Inventors the exclusive Right to their . . . Discoveries." U.S. Const. art. I, § 8, cl. 8. Contrary to petitioner's unsupported assertion that "[t]here is a longstanding and key distinction between a potentially useful scientific *discovery* and a patentable *invention*" (Pet. Br. 31), the Patent Act unequivocally states that "[t]he term 'invention' means invention or discovery." 35 U.S.C. § 100(a); *see Corning* v. *Burden*, 56 U.S. (15 How.) 252, 268 (1854) ("A new process is usually the result of discovery; a machine, of invention").

The Inventors "invent[ed] or discover[ed]" a "new and useful process"—a novel method for detecting cobalamin and folate deficiencies that often went undiagnosed using traditional methods. *See* Pet. App. 2a-3a; S.A. 12, 29. Claim 13 of the '658 patent, which recites that method, is "presumed valid." 35 U.S.C. § 282; *see Cardinal Chem. Co.* v.

Morton Int'l, Inc., 508 U.S. 83, 93 n.15 (1993). Moreover, "[t]he burden of establishing invalidity . . . shall rest on the party asserting such invalidity." 35 U.S.C. § 282; *see also Budde* v. *Harley-Davidson, Inc.*, 250 F.3d 1369, 1381 (Fed. Cir. 2001) (invalidity must be established by "clear and convincing evidence"); Pet. App. 15a. Petitioner has not met that heavy burden. Indeed, in the courts below it did not even try.

A. Subject Matter Patentability Is Not Properly Before The Court

The thrust of petitioner's submission in this Court is that "Claim 13 runs afoul" of "the 'established rule'" that "a scientific fact 'cannot be the subject of a patent.'" Pet. Br. 21 (quoting *Parker* v. *Flook*, 437 U.S. 584, 589 (1978)). Accordingly, petitioner's challenge "turns entirely on the proper construction of § 101 of the Patent Act, which describes the subject matter that is eligible for patent protection." *Flook*, 437 at 588; *see also Diehr*, 450 U.S. at 181-82, 185, 188-89, 191-92.[8] Yet, with the exception of a single cryptic footnote in its merits brief filed in this Court (Pet. Br. 19-20 n.10), petitioner has *never* so much as cited, much less invoked or discussed, Section 101 in the long history of this litigation.

Almost in passing, petitioner maintains that subject matter patentability is so important that it can be raised at any time in the litigation, even if it was not pleaded in the answer. Pet. Br. 20 & n.11. For this proposition, petitioner cites two 19th Century cases that state that non-patentability need not be pleaded. *Hill* v. *Wooster*, 132 U.S. 693, 698 (1890); *Slawson* v. *Grand Street R.R. Co.*, 107 U.S. 649, 652 (1883); *see*

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[8] Petitioner's *amici* uniformly understand its challenge to be based on Section 101. *See, e.g.*, AARP Br. 26 ("There is no patentable *invention* in Claim 13 under § 101"); ACLA Br. 16 ("[E]ven when claim 13 is viewed as a whole, it still fails to describe a 'process' within the meaning of 35 U.S.C. § 101").

also, e.g., Hendy v. *Golden State & Miners' Iron Works*, 127 U.S. 370, 375 (1888). Unfortunately for petitioner, the proposition reflected in those cases has been thrice abrogated in the last century: Not only did Congress expressly reject it in the Patent Act of 1952 as a matter of substantive patent law, but both this Court's 1937 promulgation of the Federal Rules of Civil Procedure and related rules for appellate courts also foreclose it as a matter of federal procedural law.

1. Petitioner Failed To Plead Or Prove A Non-Patentability Defense As Required By The Patent Act

During the late 19th Century when petitioner's authorities were decided, the Patent Act set forth five specific defenses that defendants in infringement actions were required to plead and prove at trial. Patent Act of 1870, ch. 230, § 61, 16 Stat. 198, 208 (July 8, 1870) (R.S. 4920). If one of the five enumerated defenses was not included in an answer, courts would not allow a party to raise the defense at a later time. *E.g., Guidet* v. *Barber*, 11 F. Cas. 103, 104 (C.C.D.N.J. 1873) (No. 5,857) (holding that a defense based on lack of novelty falls within enumerated defenses and cannot be raised if not "specified" in the answer). Significantly, the five enumerated defenses set forth in the 1870 version of the Patent Act did *not* call on defendants to plead lack of patentable subject matter as a defense. Accordingly, even courts that refused to consider one of the five enumerated defenses would excuse a defendant's failure to raise subject matter patentability in his answer. *Ibid.*

In 1952, Congress revised the Patent Act and broadened the range of defenses to be pleaded in infringement cases. New Section 282 replaced what had been Section 61 of the 1870 version of the Patent Act (R.S. 4920) with a broader, more inclusive list of defenses required to be pleaded. *See* Reviser's Notes, 1952 U.S.C.C.A.N. 2394, 2422 ("The five defenses named in R.S. 4920 are omitted and replaced by a

broader paragraph specifying defenses in general terms"). For the first time, Congress included among the defenses that "shall be pleaded" the defense of non-patentable subject matter under Section 101. 66 Stat. 792, 812 (codified at 35 U.S.C. § 282). The principle of *Slawson* and similar cases—that federal courts could consider subject matter patentability even when the defense was not raised in an answer—did not survive this substantive revision to the Patent Act.

Thus, the Patent Act now provides, in no uncertain terms, that "[t]he following shall be defenses in any action involving the validity or infringement of a patent *and shall be pleaded*: . . . Invalidity of the patent or any claim in suit on any ground specified in part II of this title as a condition for patentability." 35 U.S.C. § 282 (emphasis added). "Part II" of title 35 includes the Section 101 requirements of subject matter patentability. *Standard Oil Co.* v. *Am. Cyanamid Co.*, 774 F.2d 448, 453 (Fed. Cir. 1985).

Petitioner failed to plead a lack of subject matter patentability under Section 101 in its answer. *See* J.A. 65-70.[9] Petitioner's answer includes assertions that claim 13 is invalid for failure to satisfy Sections 102 (novelty), 103 (nonobviousness), and 112 (definiteness), but the answer does not contain any assertion that claim 13 recites unpatentable subject matter or otherwise is invalid under Section 101. J.A. 66, 64-82. Moreover, petitioner introduced no evidence on this issue at trial; the jury was not charged on subject matter patentability, and it did not return a verdict on any Section 101 defense. *See* J.A. 362-393 (complete set of jury instructions); 394-397 (special verdict form).

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[9] Although petitioner maintains without elaboration that "the issue was raised below" (Pet. Br. 17 n.9), petitioner never even mentioned Section 101 or non-patentable subject matter in the lower courts. U.S. Cert. Br. 15 ("Indeed, petitioner did not mount any challenge, under any theory, to the patentability of the claimed subject matter under Section 101").

As this Court has recognized in numerous contexts, courts must strictly enforce statutory prerequisites to litigation. *See, e.g.*, *Hallstrom* v. *Tillamook County*, 493 U.S. 20, 33 (1989); *McNeil* v. *United States*, 508 U.S. 106, 113 (1993). This is especially important where, as is the case with patents, such requirements manifestly are designed to ensure that complex questions of law, fact, science and policy are fully vetted *at trial*. As Justice Breyer has observed, it is essential that courts "mak[e] difficult science-related choices only when there has been extensive, informed development of the relevant legal and policy issues *prior* to decision." Breyer, *Genetic Advances and Legal Institutions*, 28 J. L. Med. & Ethics 23, 23 (2000). Here, because petitioner failed to include a Section 101 defense in its answer, petitioner cannot now assert that the '658 patent fails the requirements of subject matter patentability. *See, e.g.*, *Elec. Storage Battery Co.* v. *Shimadzu*, 307 U.S. 5, 16-17 (1939) (refusing to consider a validity defense that an infringer failed to plead or prove in the lower courts); *Johnson & Johnson* v. *C.B. Stenvall, Inc.*, 193 F. Supp. 128, 132 (S.D.N.Y. 1961) ("[E]ven if the defense of abandonment had merit, it was neither pleaded in the answer nor noticed in writing at least 30 days before the trial as required by 35 U.S.C. § 282, and therefore is not entitled to consideration").

2. Petitioner's Failure To Plead A Non-Patentability Defense Runs Afoul Of General Pleading Rules

Petitioner's belated attempt to raise the Section 101 patentability defense also violates the Federal Rules of Civil Procedure, which expressly require defendants to plead "any . . . matter constituting an avoidance or affirmative defense." Fed. R. Civ. P. 8(c). As Professors Wright and Miller have observed, this rule has led the lower courts "virtually universal[ly]" to conclude that "a failure to plead an affirmative defense . . . results in the waiver of that defense and its exclu-

sion from the case." 5 *Federal Practice & Procedure* § 1278 (3d ed. 2004). Barely two years ago, in *Kontrick* v. *Ryan*, 540 U.S. 443 (2004), this Court agreed.

This Court held in *Kontrick* that a debtor forfeited his right to rely on a defense by failing to raise the issue in his answer or, indeed, at any time before the trial court reached the merits of the case. *See* 540 U.S. at 458-60. The Court made clear that "under the Bankruptcy Rules *as under the Civil Rules*, a defense is lost if it is not included in the answer or amended answer" or, "at the latest, 'at the trial on the merits.'" *Id.* at 459-60 (quoting Fed. R. Civ. P. 12(h)(2)) (emphasis added); see also *Hormel*, 312 U.S. at 556 ("our procedural scheme contemplates that parties shall come to issue in the trial forum vested with authority to determine questions of fact"). Here, as in *Kontrick*, petitioner is barred from raising the Section 101 patentability affirmative defense after it lost its case on the merits in the district court.

Petitioner further cemented the forfeiture of the Section 101 defense by failing to raise the issue at all until the case reached the merits stage at this Court. *See Helvering* v. *Tex-Penn Oil Co.*, 300 U.S. 481, 497-98 (1937) (petitioner "sought no ruling upon the question from the board or the lower court and is therefore not entitled to have it decided here"). Petitioner, represented by sophisticated counsel throughout this litigation, had multiple opportunities to attempt to inject the Section 101 invalidity argument into the case, and with each pleading, brief, or other submission petitioner knowingly bypassed that argument. At trial, petitioner put forth evidence and argument to support the invalidity arguments it had pleaded, but never mentioned Section 101 or subject matter patentability. No witness testified on the issue. No jury instruction was given regarding patentable subject matter or Section 101. Petitioner's pre-submission and post-trial motions for judgment as a matter of law similarly failed to raise a Section 101 defense. Dkt. 249, 250. As this Court recently reaffirmed in *Unitherm Food Systems, Inc.* v.

Swift-Eckrich, Inc., No. 04-597, slip op. 5-9, this last failure *by itself* was sufficient to deprive the Federal Circuit and this Court of any "power" to grant petitioner *any* relief (*i.e.*, reversal or a new trial), even if the Section 101 argument had been properly raised on appeal thereafter. *See also Cone* v. *W. Va. Pulp & Paper Co.*, 330 U.S. 212, 217-18 (1947); *Hopp v. City of Pittsburgh*, 194 F.3d 434, 440 (3d Cir. 1999) (Alito, J.).

Petitioner, of course, did *not* thereafter appeal any issue related to Section 101 or subject matter patentability to the Federal Circuit. Instead, petitioner reiterated its invalidity arguments under Sections 102, 103, and 112; it made no mention of Section 101 in its opening brief, its reply brief, or its petition for rehearing. In the court below, as in every other court of appeals, petitioner's failure to brief the claim it now seeks to present to this Court is, in and of itself, an independent basis for deeming that claim forfeited. *E.g.*, *Pandrol USA, LP* v. *Airboss Ry. Prods., Inc.*, 320 F.3d 1354, 1366 n.3 (Fed. Cir. 2003); *Becton Dickinson & Co.* v. *C.R. Bard, Inc.*, 922 F.2d 792, 800 (Fed. Cir. 1990).[10]

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[10] Petitioner clings to a passage in its opening Federal Circuit brief to suggest that it raised the issue below. Pet. Br. 14 (quoting Pet. C.A. Br. 41). The desperate implausibility of this contention can scarcely be overstated. Although petitioner cited *Diehr* for the proposition that natural phenomena are excluded from patent protection, it did *not* challenge the validity of the patent under Section 101. *See* Pet. C.A. Br. 38. Indeed, after *respondents* pointed out in their answering Federal Circuit brief that petitioner had waived any conceivable Section 101 argument (Resp. C.A. Br. 71), petitioner said nothing further on the point. Thus, not only did petitioner fail to make an affirmative Section 101 argument, it also tellingly declined to engage on the question when respondents noted the waiver of any such issue.

3. This Court's Own Rules Preclude Consideration Of A Defense Of Non-Patentability

Petitioner nonetheless contends that this Court should review the Section 101 issue because that issue is "fairly included in Question 3." Pet. Br. 17 n.9. Even if that were true, it would not excuse the fact that the patentability issue was never raised in, or decided by, the courts below. *See, e.g., Bankers Life & Cas. Co.* v. *Crenshaw*, 486 U.S. 71, 76-77 (1988) (treating issue "as if contained in a petition for a writ of certiorari," but "declin[ing] to decide the merits of the issue"). This Court is not a tribunal of "first view." *Adarand Constructors, Inc.* v. *Mineta*, 534 U.S. 103, 110 (2001) (quoting *Matsushita Elec. Indus. Co.* v. *Epstein*, 516 U.S. 367, 399 (1996) (opinion of Ginsburg, J.)).

In any event, the Section 101 issue is not "fairly included" in Question 3, which seeks review of the lower courts' determinations that claim 13 meets the requirements of Section 112. As this Court made clear in *Diehr*, Section 101's subject matter eligibility requirements are wholly *separate* from those set forth elsewhere, such as the novelty requirement of Section 102, the nonobviousness requirement of Section 103, or, by logical extension, the descriptive requirements of Section 112. 450 U.S. at 189-91; *see* U.S. Br. 14 (The "limitation under Section 101" on monopolizing natural phenomena "is entirely separate and distinct from the requirements of Section 112"). In light of *Diehr*, any Section 101 issue is sufficiently tangential to the Section 112 question presented as to make subject matter patentability *not* "fairly included therein." *Yee* v. *City of Escondido*, 503 U.S. 519, 537 (1992). Section 112's requirements and Section 101's requirements may "exist side by side," but "neither encompass[es] the other." *Ibid.*

Nor do any passing arguments in the *text* of the petition concerning the potential *consequences* of upholding the Fed-

eral Circuit's Section 112 rulings somehow serve to bring the Section 101 issue within Question 3. *See* U.S. Br. 15-16. To begin with, petitioner mentioned *Diehr* only to argue that it should not be held liable for *induced* infringement because the patent allegedly incorporates a "scientific fact"—a question on which this Court denied certiorari. Pet. 18-19. Moreover, even if a separate Section 101 invalidity argument *had* been included in the text of the petition—which it was not—that would not be sufficient to bring the issue before the Court under Rule 14.1(a), which "requires that a subsidiary question be fairly included in the *question presented* for [the Court's] review." *Izumi Seimitsu Kogyo Kabushiki Kaisha* v. *U.S. Philips Corp.*, 510 U.S. 27, 31 n.5 (1993).

In fact, it is abundantly clear that a Section 101 argument did not even occur to petitioner until the Court *sua sponte* sought the Solicitor General's views on such an argument, well after the petition and the opposition were filed. *See* Resp. Br. in No. 04-1579, at 2-3 n.*. For that reason, petitioner is wrong to contend that respondents should have opposed certiorari in this case on the ground that no Section 101 issue is properly before the Court. As the Solicitor General recognizes, nothing in this Court's rules required that respondents object, preemptively, to an issue that is not encompassed within any question presented. U.S. Br. 17; *see City of Springfield* v. *Kibbe*, 480 U.S. 257, 260 (1987). Because petitioner's Section 101 argument is not fairly encompassed within the question presented, and was neither pressed nor passed upon below, this Court should decline to consider it at this late date. And because that issue is the principal focus of the briefs filed by petitioner and its *amici*, this Court may wish to consider dismissing the writ of certiorari. *See, e.g.*, *Adarand*, 534 U.S. at 111; *City of Springfield*, 480 U.S. at 259-60.[11]

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[11] Dismissal would be particularly appropriate because the '658 patent will expire in July 2007. The Section 101 issue that

B. The '658 Patent Claims Patentable Subject Matter

Assuming *arguendo* that the issue of subject matter patentability is properly before the Court, claim 13 of the '658 patent easily satisfies the requirements of Section 101. The Inventors discovered what could be considered, standing alone, a natural phenomenon, and then put that discovery to practical use by inventing a method for diagnosing cobalamin or folate deficiencies. In a line of cases culminating with *Diehr*, this Court has held that such "an *application* of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection." 450 U.S. at 187 (emphasis in original); *see also, e.g., Chakrabarty*, 447 U.S. at 309-10; *Mackay Radio & Tel. Co.* v. *Radio Corp. of Am.*, 306 U.S. 86, 94 (1939); *Le Roy* v. *Tatham*, 55 U.S. (14 How.) 156 (1853).

Since *Diehr* was decided in 1981, the Federal Circuit has been the final arbiter on questions of subject matter patentability. During that time, the Federal Circuit has applied *Diehr* in many cases to determine whether claimed processes employing natural phenomena fall within the statutory subject matter set forth in Section 101. *See, e.g., AT&T Corp.* v. *Excel Communications, Inc.*, 172 F.3d 1352 (Fed. Cir. 1999); *State Street Bank & Trust Co.* v. *Signature Fin. Group, Inc.*,

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petitioner failed to raise during five years of litigation would have little practical significance just a year after this Term ends. At that time, the injunction entered by the district court (which has been stayed pending resolution of appellate proceedings) will also terminate. Although petitioner and some *amici* express concern with the scope of that injunction (*see* U.S. Br. 23-24, 29; Pet. Br. 36-37; AARP Br. 16), that concern—like petitioner's contention (Br. 48 n.28) that "the injunction should be vacated in light of whatever standard the Court announces in *eBay, Inc.* v. *MercExchange, L.L.C.*, No. 05-130"—is misplaced: Petitioner did not challenge the injunction in its petition, and the Court did not grant review of the scope of the injunction.

149 F.3d 1368 (Fed. Cir. 1998); *In re Alappat*, 33 F.3d 1526 (Fed. Cir. 1994) (en banc). Today, it is clear that Section 101's subject matter requirements are met if a natural phenomenon incorporated in the claimed invention "has been reduced to some practical application rendering it 'useful.'" *Excel*, 172 F.3d at 1356-57; *accord Alappat*, 33 F.3d at 1543-44; *State Street*, 149 F.3d 1373.

The PTO has followed this Court's and the Federal Circuit's precedent regarding Section 101, and its *Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility*, 1300 Off. Gaz. 142 (Nov. 22, 2005)—which "are believed to be fully consistent with binding precedent of the Supreme Court, the Federal Circuit and the Federal Circuit's predecessor courts" (App., *infra*, 5a)—are highly instructive.[12] Those *Guidelines* set forth the methodology that patent examiners are to use in determining whether patent applications claim statutory subject matter. *See* App., *infra*, 20a (flowchart summarizing steps in the analysis). As they are entitled at the very least to deference under *Skidmore* v. *Swift & Co.*, 323 U.S. 134, 140 (1944), the *Guidelines* (which petitioner fails even to mention) also provide a useful framework for judicial analysis of subject matter patentability.

1. The Claimed Invention Falls Within A Category Enumerated In 35 U.S.C. § 101

The expansive language of Section 101 allows a patent on "anything under the sun that is made by man." *Chakrabarty*, 447 U.S. at 308-09 (quoting S. Rep. No. 1979, at 5

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[12] Because this volume of the *Official Gazette* is not yet available in print, we have reproduced pertinent portions of the PTO's *Subject Matter Eligibility Guidelines* in the appendix to this brief. *See also* 70 Fed. Reg. 75,451, 75,452 (Dec. 20, 2005) (requesting public comment on the *Guidelines*).

(1952), H.R. Rep. No. 1923, at 6 (1952)). In addition to machines, manufactures, and compositions of matter, Section 101 makes "processes" patentable. "A process is a mode of treatment of certain materials to produce a given result." *Cochrane* v. *Deener*, 94 U.S. 780, 788 (1877); *accord Diehr*, 450 U.S. at 183. Claim 13 fits this description precisely: It claims a process for treating certain materials (*i.e.*, assaying body fluids and correlating the assay results with vitamin status) to achieve a desired result (*i.e.*, detecting cobalamin or folate deficiencies).

Contrary to petitioner's assertion (Br. 23), it is of no moment that the patented process can be practiced using an assay procedure that may have been known previously.[13]

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[13] The government briefly questions whether claim 13 might be invalid under 35 U.S.C. § 102 (anticipation) "because the claim effectively prevents doctors from using previously known assay methods to measure total homocysteine for *any* purpose, even if the purpose was not to diagnose cobalamin or folate deficiency." U.S. Br. 28. There are indeed other purposes for assaying for total homocysteine, such as detecting certain inherited enzyme defects (which are relatively rare). S.A. 14 ("When homocysteine levels are elevated in individuals *without inherited defects*, at least one of folate or cobalamin is deficient") (emphasis added); *see also* S.A. 11; J.A. 137; C.A. App. 9648, 9697, 5552. The injunction in this case does not prevent "doctors" from making use of such assays. Rather, it precludes *petitioner*—which is not a doctor—from assaying for total homocysteine because *petitioner* failed to offer any evidence that any of *its* assays were for any of these other purposes. In any event, as the government concedes, the anticipation issue is "not before this Court." U.S. Br. 28. At trial, petitioner raised an anticipation defense, which was rejected by the jury. J.A. 396-397. Petitioner reiterated its anticipation defense on appeal, where it was rejected by the Federal Circuit. Pet. App. 18a-19a. Petitioner did not seek certiorari on the anticipation issue, so it has been abandoned. *Posters 'N' Things, Ltd.* v. *United States*, 511 U.S. 513, 527 (1994). There is no reason, or basis, to consider or decide an issue raised only in passing by the United States as *amicus curiae*. *See, e.g.*, *United Parcel Service, Inc.* v. *Mitchell*,

"The process requires that certain things should be done with certain substances, and in a certain order; but the tools to be used in doing this may be of secondary consequence." *Cochrane*, 94 U.S. at 788. Claim 13 teaches that doing "certain things" (assaying and correlating) with "certain substances" (body fluids) in a "certain order" (sequentially) will achieve a desired result—the diagnosis of vitamin deficiency. That is the essence of a patentable method. *Corning*, 56 U.S. (15 How.) at 268 ("It is when the term process is used to represent the means or method of producing a result that it is patentable").

It is therefore clear that claim 13 recites a process, and thus that it is drawn to statutory subject matter. The remaining question is whether the invention falls within one of the exceptions that this Court has recognized to Section 101's intentionally broad scope.

2. The Claimed Invention Does Not Fall Within A Judicial Exception To Section 101

"This Court has . . . recognized limits to § 101 and every discovery is not embraced within the statutory terms. Excluded from such patent protection are laws of nature, natural phenomena, and abstract ideas." *Diehr*, 450 U.S. at 185. These categories constitute "judicially created exception[s] to § 101." *Alappat*, 33 F.3d at 1542.

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451 U.S. 56, 60 n.2 (1981). In any event, the government's conjecture is mistaken. The PTO in fact rejected a previous iteration of claim 13 "as being anticipated" by prior art assays "[i]n the absence of a correlation step." J.A. 285. In response, the Inventors amended claim 13 "to recite a second step of correlating an elevated level of total homocysteine with a deficiency of cobalamin or folate." J.A. 290. The PTO then *withdrew* its Section 102 objection and allowed the patent as amended to issue. *See* Pet. App. 9a (summarizing prosecution history).

The correlation between total homocysteine and deficiencies in cobalamin and folate that the Inventors discovered could be considered, standing alone, a "natural phenomenon" in the literal sense: It is an observable aspect of biochemistry in at least some human populations. Of course, in the physical world "[e]verything that happens may be deemed 'the work of nature.'" *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 135 (1948) (Frankfurter, J., concurring). The Court has held that "[h]e who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes." *Id.* at 130 (majority opinion). But respondents do not claim a monopoly to the correlation discovered by the Inventors. Rather, claim 13 recites a *method* for using the correlation as a sequential step toward achieving the desirable end of diagnosing vitamin deficiencies. It is clearly patentable under existing law.

a. The Claimed Invention Covers A Practical Application Of A Natural Phenomenon

In *Flook*, the Court took a restrictive view of patentable subject matter and concluded that a claimed invention must include a novel or inventive aspect separate and apart from the discovery of a natural phenomenon itself. *See* 437 U.S. at 593-95. While petitioner repeatedly invokes this aspect of *Flook* (*e.g.*, Pet. Br. 28, 31), petitioner fails to acknowledge that the *Flook* approach was short-lived.

In *Diehr*, this Court retreated from language in *Flook* and made clear that "[t]he 'novelty' of any element or steps in a process, or even of the process itself, *is of no relevance* in determining whether the subject matter of a claim falls within the § 101 categories of possibly patentable subject matter." *Diehr*, 450 U.S. at 188-89 (emphasis added). Instead, the question "of whether a particular invention is novel is 'wholly apart from whether the invention falls into a category of statutory subject matter.'" *Id.* at 190 (quoting *In re*

Bergy, 596 F.2d 952, 961 (C.C.P.A. 1979), *vacated as moot*, 444 U.S. 1028 (1980)).[14] Thus, while a mathematical equation or law of nature "is not patentable in isolation," when incorporated as part of a process that yields a more efficient or useful end, "that process is at the very least not barred at the threshold by § 101." *Id.* at 188; *see also id.* at 187.

Although petitioner would have this Court apply the narrow view of subject matter patentability suggested by language in *Flook*, the Federal Circuit has since recognized—correctly—that *Flook* was "in part superseded" (*Arrhythmia Research Tech., Inc.* v. *Corazonix Corp.*, 958 F.2d 1053, 1057 n.4 (Fed. Cir. 1992)) and "expressly limited" (*Excel*, 172 F.3d at 1356) by *Diehr*. *See* U.S. Cert. Br. 11-15. Thus, a natural phenomenon "in the abstract" does not constitute patentable subject matter, but a claimed invention does meet Section 101's subject matter requirements when the phenomenon "has been reduced to some practical application rendering it 'useful.'" *Excel*, 172 F.3d at 1356-57; *accord Alappat*, 33 F.3d at 1543-44; *State Street*, 149 F.3d 1373.

Like the Federal Circuit, the PTO has adhered to *Diehr*. *See* U.S. Br. 21-22 n.4. Its *Guidelines* instruct patent examiners that a "practical application" of an abstract idea, law of nature, or natural phenomenon is patentable subject matter within the meaning of Section 101 "if the claimed invention

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[14] Although petitioner half-heartedly suggests that the Inventors did not in fact invent the process claimed in the patent (Pet. Br. 4 & n.2), failure to meet the requirements of Sections 102 or 103 "does not affect the determination" whether the patent "recite[s] subject matter which [is] eligible for patent protection under § 101." *Diehr*, 450 U.S. at 190-91 (internal quotation omitted). In any event, respondents established the novelty of the inventive method in the courts below (*see* Resp. C.A. Br. 55-60), and the Federal Circuit affirmed the jury's findings that petitioner had failed to prove anticipation or obviousness. Pet. App. 18a-21a. Petitioner's failure to challenge those factual findings in this Court renders its skewed recitation of history completely immaterial.

physically transforms an article or physical object to a different state or thing, *or* if the claimed invention otherwise produces a useful, concrete, and tangible result." App., *infra*, 5a (emphasis added). Under either of the independently sufficient parts of that test, claim 13 plainly passes the Section 101 threshold.[15]

i. Claim 13 Entails A Physical Transformation Of Matter

"Transformation and reduction of an article 'to a different state or thing' is the clue to patentability of a process claim that does not include particular machines." *Gottschalk* v. *Benson*, 409 U.S. 63, 70 (1972); *see Cochrane*, 94 U.S. at 788 ("A process is . . . an act, or a series of acts, performed upon the subject-matter to be transformed and reduced to a different state or thing"). In *Diehr*, the Court held that "when a claim containing a mathematical formula implements or applies that formula in a structure or process which, when considered as a whole, is performing a function which the patent laws were designed to protect (*e.g.*, transforming or reducing an article to a different state or thing), then the claim satisfies the requirements of § 101." 450 U.S. at 192.

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[15] Although petitioner maintains (Br. 17, 23-24) that claim 13 involves no "post-solution activity," petitioner's arguments in this regard are misdirected. This Court noted in *Diehr* that "insignificant postsolution activity will not transform an unpatentable principle into a patentable process" (*Diehr*, 450 U.S. at 191-92), but the Court has never held that "post-solution activity" is a prerequisite to patentability. Nor has such a requirement been imposed by the Federal Circuit or the PTO. Indeed, it is not clear that the concept of "post-*solution* activity" has any applicability outside the area of mathematical algorithms (which, by definition, involve a "solution"). *See Flook*, 437 U.S. at 590. Here, because claim 13 undoubtedly meets the subject matter eligibility requirements that this Court *has* imposed, the issue of "post-solution activity" (or, for that matter, "pre-solution activity") simply has no bearing on this case.

The PTO's *Guidelines* recognize that the transformation of matter, in itself, is dispositive of the Section 101 question:

> The examiner first shall review the claim and determine if it provides a transformation or reduction of an article to a different state or thing. If the examiner finds such a transformation or reduction, *the examiner shall end the inquiry and find that the claim meets the statutory requirement of 35 U.S.C. § 101.*

App., *infra*, 14a (emphasis added). Because the invention of claim 13 *requires* the transformation of matter (*i.e.*, blood or other body fluid) in order to diagnose vitamin deficiencies, it is patentable under Section 101.

Petitioner states, without citation, that "Claim 13 recites no such transformative method" because "the assaying step does not direct a practitioner to transform anything." Pet. Br. 27; *see also, e.g.*, CCIA Br. 4 n.4 (asserting that claim 13 "produce[s] no transformation"). That is simply wrong as a matter of both biochemistry and the undisputed evidence.

The assaying step requires "assaying a body fluid for an elevated level of total homocysteine." S.A. 30. It is undisputed that total homocysteine includes at least four species of homocysteine, three of which do not exist in free form. Pet. Br. 2-3 n.1. As the patent itself explains, "[i]n the presence of proteins, . . . homocysteine . . . form[s] complexes with free sulfhydryl groups on the protein molecule; in samples derived from tissues, such protein complexes may tie up most of the . . . homocysteine present." S.A. 13. As a result, "*[r]eduction is required* for release and subsequent assay of protein bound sulfhydryl compounds." *Ibid.* (emphasis added). Or, as an article co-authored by the Inventors explains, "[d]etermination of total Hcy [homocysteine] in plasma/serum *requires the reduction* of the disulfide bond between Hcy and other thiols or albumin." J.A. 262 (emphasis added); *see also* J.A. 247.

Thus, as the Solicitor General has correctly recognized, "the various methods of assaying for total homocysteine that are described in the record entail significant physical or chemical alteration of a sample of blood or other bodily fluid." U.S. Br. 21 n.4. Petitioner has identified no assay method that does *not* involve the transformation of matter, and given the biochemistry involved, no such assay could exist. Thus, petitioner has not carried its burden of proving, by clear and convincing evidence, that claim 13 is invalid because it could be practiced without transforming matter. Nothing more is required under *Diehr* to sustain the patent.[16]

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[16] *Amicus* ACLA wrongly contends (Br. 18) that the transformation that is an integral part of the inventive diagnostic method is insufficient because it is a "means to the end" and "does precisely the reverse" of the patent at issue in *Diehr*. ACLA's novel distinction, however, has no support in the law. Claim 13 sets forth a two-step process, which indisputably cannot be completed without the physical transformation of matter. Contrary to ACLA's theory, *Diehr* says nothing about whether the physical transformation has to be the *final* step in a claimed process; rather, as the PTO *Guidelines* reflect, it holds that if a process performs a physical transformation "function" it passes muster under Section 101. *Diehr*, 450 U.S. at 192. Claim 13 does so. And because claim 13 requires the transformation of matter, petitioner's attempt to liken this case to *Funk Brothers* (Br. 21) is mistaken. In *Funk Brothers*, the Court held that "aggregation of species [of bacteria] fell short of invention within the meaning of the patent statutes" because no transformation had been effected: "The combination of species produces no new bacteria, no change in the six species of bacteria, and no enlargement in the range of their utility." 333 U.S. at 131. The Court has since held that a "nonnaturally occurring" bacterium could be patented because it had "markedly different characteristics from any found in nature." *Chakrabarty*, 447 U.S. at 310. The Inventors' diagnostic method likewise is not to be found in nature, but rather is "a product of human ingenuity" (*id.* at 309) that meets every extant test for subject matter patentability.

ii. The Method Of Claim 13 Produces A Useful, Tangible, And Concrete Result

Claim 13 also passes the Section 101 threshold for the separately sufficient reason that it produces a useful, tangible, and concrete result. *See* App., *infra*, 15a. Although natural phenomena are not patentable subject matter when they are presented as "merely abstract ideas constituting disembodied concepts or truths that are not 'useful,'" when natural phenomena are incorporated in a claimed invention as part of a process that produces a "useful, concrete, and tangible result," the invention satisfies Section 101. *State Street*, 149 F.3d at 1373, 1375; *Alappat*, 33 F.3d at 1544; *Excel*, 172 F.3d at 1360. The "result" produced under the two-step process set forth in claim 13 is a diagnosis of a condition of the human body, namely the detection of cobalamin or folate deficiencies; this diagnostic result plainly meets the *State Street* factors.

The result produced by the inventive method is clearly "useful" in that it detects a potentially dangerous medical condition and improves the patient's chances of receiving proper treatment. *See, e.g., Arrhythmia Research*, 958 F.2d at 1059-60 (holding that process claims setting forth "a method of analyzing electrocardiograph signals in order to determine a specified heart activity" are directed to statutory subject matter); *id.* at 1066 (Rader, J., concurring) (a method "for detecting the risk of a heart attack" qualifies as statutory subject matter under Section 101). In fact, petitioner concedes, as it must, that claim 13 sets forth a "practical use" by enabling the "detect[ion of] vitamin deficiencies." Pet. Br. 27.

The result produced under claim 13 is also "tangible," which the PTO defines as the opposite of "abstract." App., *infra*, 16a. Unless properly diagnosed, a patient suffering from cobalamin or folate deficiencies may not receive proper supplements to treat his or her condition. Proper medical di-

agnoses have tangible, real-life consequences and are far from "abstract." As with the method patent at issue in *Arrhythmia Research*, claim 13 does not "disclose mere abstract ideas, but a practical and potentially life-saving process." 958 F.2d at 1065-66 (Rader, J., concurring); *see also State Street* 149 F.3d at 1373 (explaining that *Arrhythmia Research* was decided consistently with the "useful, tangible, and concrete result" test); *accord Excel*, 172 F.3d at 1359.

Finally, claim 13 produces a "concrete" result. The PTO defines "concrete" as the opposite of "unrepeatable or unpredictable." App., *infra*, 17a. One of the great benefits of the process set forth in claim 13 is that it yields predictable, repeatable results. S.A. 27-28; J.A. 85, 177. By inventing a method that accurately and repetitively detects the presence or absence of cobalamin or folate deficiencies, the Inventors have added an important diagnostic technique to the arsenal of medical practitioners.

Petitioner has never disputed that claim 13 produces a useful, tangible, and concrete result. Instead, petitioner chooses to ignore the existence of that standard altogether, and clings to language in *Flook* to contend that because the usefulness of the patents at issue in that case "did not save them," it must be true that "specifying one practical use for a scientific correlation does not render a patent claim valid." Pet. Br. 28. That view was rejected in *Diehr*, however, which provided that when a process employing a natural phenomenon results in a practical use, it *does* fall within Section 101. *See Diehr*, 450 U.S. at 188, 192; *State Street*, 149 F.3d at 1375. Petitioner offers no basis for this Court to resurrect the superseded aspects of *Flook* and does not even attempt to square its theory of unpatentability with the rule developed in *Diehr*, applied in the Federal Circuit, and reflected in the PTO's *Guidelines*.[17]

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[17] Petitioner's invocation (Br. 24-25 & n.13) of *In re Grams*, 888 F.2d 835 (Fed. Cir. 1989), does not improve its position.

Nor does petitioner's repeated contention that the patent is invalid because it allegedly precludes doctors from "thinking about" test results (*e.g.*, Pet. Br. 22), provide reason to question the patentability of claim 13. Aside from the fact that a computer could presumably be programmed to perform the correlating step on the results of an assay, the so-called "mental steps test" that petitioner and its amici seek to invoke (Pet. Br. 27 n.14; CCIA Br. 5; AARP Br. 21) was long ago repudiated as an appropriate measure of patentability. *See, e.g.*, App., *infra*, 21a-22a (citing *In re Musgrave*, 431 F.2d 882, 893 (C.C.P.A. 1970)). Thus, even "[i]f all the steps of a claimed process can be carried out in the human mind," the proper inquiry remains "whether the claimed process produces a useful, tangible, and concrete result," as "set forth in *State Street*." *Id.*

In any event, claim 13 is only infringed when the assaying and correlating steps are *both* performed, sequentially, for the purpose of diagnosing vitamin deficiencies. The act of assaying body fluids for total homocysteine for reasons other than diagnosing vitamin deficiencies would not infringe. Nor would the act of correlating alone, or what petitioner calls "thinking about" the relationship between total homocysteine and vitamin deficiencies.[18]

Grams has been expressly disapproved by the Federal Circuit (*Excel*, 172 F.3d at 1360), and no court has cited it since.

[18] Petitioner was found to infringe the patent because petitioner marketed its total homocysteine assays for use in diagnosing vitamin deficiencies via the method of claim 13. J.A. 173, 189-195, 255-256, 257-258, 259-261; *see MGM Studios Inc.* v. *Grokster, Ltd.*, 125 S. Ct. 2764, 2779 (2005) ("The classic case of direct evidence of unlawful purpose occurs when one induces commission of infringement by another, or entices or persuades another to infringe, as by advertising") (internal quotation and citation omitted). Whether other persons or entities infringe the '658 patent is a separate question on which no evidence was presented below. Petitioner attempts to dispute this by noting (Br. 15) that one of the

b. The Claimed Invention Does Not "Preempt" Public Use Of Any Natural Phenomenon

As just demonstrated, claim 13 recites a practical application of the correlation between elevated total homocysteine and cobalamin and folate deficiencies discovered by the Inventors. The only remaining question on patentability is whether claim 13, as construed by the lower courts, is so sweeping as to "preempt" public use of that correlation. *Diehr*, 450 U.S. at 191; *see* App., *infra*, 15a. A patent sweeps too broadly if it comprises every "substantial practical application" of a natural phenomenon, because it "in practical effect would be a patent on the [phenomenon] itself." *Benson*, 409 U.S. at 71-72.

Respondents do not seek, and the '658 patent does not claim, a monopoly on the correlation between total homocysteine and vitamin deficiencies. Rather, the Inventors have patented a particular *application* of that correlation, when used as a sequential step in a diagnostic method. In this regard, the Inventors here are analogous to the patentees in *Diehr*: "Their process admittedly employs a well-known mathematical equation, but they do not seek to pre-empt use of that equation. Rather, they seek only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process." 450 U.S. at 187.[19]

Inventors "testified that it would be malpractice for a doctor to receive a total homocysteine assay without determining cobalamin/folate deficiency." Pet. App. 14a. What the Inventor actually said was that it would be malpractice to "fail to treat in response to [a] high homocysteine level." J.A. 106. She was not asked whether the purpose of the hypothetical assay was to detect cobalamin and folate deficiencies or, for example, to instead diagnose an inherited enzyme defect. *See* note 13, *supra*.

[19] For this reason, petitioner errs in attempting to equate the '658 patent with Samuel Morse's effort to monopolize "electro-

The government asserts, incorrectly, that "claim 13 appears to cover all substantial practical applications of the natural phenomenon." U.S. Br. 24. That assertion rests entirely on the jury's finding in connection with the contributory infringement claim (which was not considered by the court of appeals) "that no *substantial* non-infringing uses *of the total homocysteine assays* had been proven on the trial record." *Id.* at 23 (emphases added).[20] But the "natural phenomenon" at issue in this case is *not* the assay performed by petitioner, but rather the *correlation* between total homocysteine and vitamin deficiencies—as the government elsewhere acknowledges. *Id.* at 19. The jury made *no* finding that claim 13 covers substantially all practical applications of that correlation.

Contrary to the government's suggestion, there is no reason to "vacate and remand for further proceedings to determine whether all substantial practical applications of the correlation are claimed by the patent." U.S. Br. 26-27. As the government acknowledges, *petitioner* bears the burden of proving that no such applications exist. *Id.* at 24. Yet petitioner offers only the bare assertion that "[t]he scientific

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magnetism." Pet. Br. 35 (quoting *O'Reilly* v. *Morse*, 56 U.S. (15 How.) 62, 112 (1853)). Whereas Morse claimed all uses of a natural phenomenon, the '658 patent claims just one. The more apt analogy is Alexander Graham Bell's telephone patent. *Dolbear* v. *Am. Bell Tel. Co.*, 126 U.S. 1, 535 (1888) ("It may be that electricity cannot be used at all for the transmission of speech except in the way Bell has discovered, and that therefore, practically, his patent gives him its exclusive use for that purpose, but that does not make his claim one for the use of electricity distinct from the particular process with which it is connected in his patent").

[20] Although the jury found that there were no substantial non-infringing uses for the assays performed *by petitioner* (a for-profit provider of test results), it made no such finding as to total homocysteine assays performed by others for a different purpose (such as detecting an inherited enzyme defect).

principle that elevated homocysteine is associated with vitamin deficiencies is substantially covered by Claim 13" (Pet. Br. 28), citing *nothing* in the record—let alone the clear and convincing evidence that would be required to prevail. If the record were entirely silent, then the statutory presumption of validity would require affirmance of the judgment. This Court does not sit to order remands for consideration of issues that the petitioner failed to raise at any previous stage of the litigation. *E.g.*, *Pasquantino* v. *United States*, 125 S. Ct. 1766, 1781 n.14 (2005); *Yee*, 503 U.S. at 533.[21]

In any event, the record in fact discloses several non-infringing uses of the correlation. One such use is suggested by a study where the authors recommend cobalamin and folate supplements for all men over 45, and all women over 55, in order to reduce and prevent elevated total homocysteine levels (which are associated with heart disease and other illnesses), *without* first assaying total homocysteine in any patient. J.A. 107-108, 204-205; C.A. App. 4687-4688, 8711-8717. The authors estimated that this treatment strategy would save hundreds of thousands of lives, and billions

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[21] Although petitioner now asks this Court to hold the patent invalid and "reverse the judgment against [petitioner] in its entirety" (Pet. Br. 19), an order directing entry of judgment against respondents is obviously precluded by the Seventh Amendment because no jury has found the *factual* predicates to a Section 101 defense. *Dimick* v. *Schiedt*, 293 U.S. 474, 486-87 (1935). Moreover, on the record in this case it would be inconceivable for the Court to remand for further proceedings. *Unitherm*, slip op. 7 ("This Court's observations about the necessity of a postverdict motion under Rule 50(b), and the benefits of the district court's input at that stage, apply with equal force whether a party is seeking judgment as a matter of law or simply a new trial"). Indeed, petitioner's request to be placed in a better position than it would have occupied had it complied with all applicable substantive and procedural rules speaks volumes not only of the weakness of its position but also of its misunderstanding of the role of this Court in our judicial system.

of dollars, over a ten-year period. J.A. 205. In another study, the authors determined that the toxicity of a chemotherapy treatment appeared related to patients' levels of total homocysteine. Aware of the correlation discovered by these Inventors, the authors recommended administering supplemental cobalamin and folate, thereby lowering the toxicity of an important drug that "has demonstrated promising clinical activity in a wide variety of solid tumors, including non-small cell lung, breast, mesothelioma, colorectal, pancreatic, gastric, bladder, cervix, and head and neck." C.A. App. 9763. Cancer patients who receive this drug today receive it in conjunction with supplemental cobalamin and folate as recommended by these authors. C.A. App. 4713-4714, 9763-9778.[22] Treating patients with vitamin supplements to reduce the risk of heart attack or the toxicity of a cancer drug, without first assaying for total homocysteine, constitute uses of the correlation at issue that do not infringe the patent.

Moreover, a number of other non-infringing uses of the correlation discovered by the Inventors appear in the medical literature, which is readily available to persons skilled in the art. As just one example, a recent study posited that elevated total homocysteine could play a role in the incidence of bone fractures sustained by stroke victims. To test this hypothesis, half of a control group were given placebos while the other half received cobalamin and folate supplements; the patients who received vitamin supplements suffered far fewer fractures than the ones who did not. *See* Sato, *et al.*, *Effect of Folate and Mecobalamin on Hip Fractures in Patients with Stroke*, 293 J. Am. Med. Assoc. 1082 (2005). As a practitioner's resource recently summarized this study, "it is reason-

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[22] Since the record in this case was closed, the FDA has approved this drug for the treatment of mesothelioma, an asbestos-related cancer, as well as to treat the most common form of lung cancer. *See* Rollins & Lindley, *Pemetrexed: A Multitargeted Antifolate*, 27 Clinical Therapeutics 1343 (2005).

able to give these inexpensive and safe vitamins [B_{12} and folate] to patients with stroke." American College of Physicians Journal Club, *Folate plus vitamin B_{12} reduced hip fractures in patients with poststroke hemiplegia*, Vol. 143 No. 2 (Sept./Oct. 2005). Treating stroke victims with vitamin supplements to reduce fractures, without first assaying for total homocysteine, is yet another use of the correlation discovered by the Inventors that does not infringe the '658 patent.

Many more substantial practical applications of the correlation that do not infringe claim 13 are undoubtedly being practiced currently, or could be developed in the future, but these examples will suffice to show that petitioner has not carried *its* burden of proving, by clear and convincing evidence, that such uses are absent and the patent is therefore invalid. Rather, the examples confirm claim 13's validity under the government's own analysis. U.S. Br. 24 n.5, 26. The patent is not "preemptive" within the meaning of *Diehr* and *Benson*.

C. The Sea Change Sought By Petitioner Would Be Unnecessarily Disruptive To The Patent System

As demonstrated above, claim 13 of the '658 patent meets the subject matter eligibility requirements of current law, as enunciated by this Court (in *Diehr*), the Federal Circuit (in *State Street*, *Excel*, and *Alappat*), and the PTO (in its interim *Guidelines*). Thus, in order to grant petitioner any relief on the subject matter patentability argument that it has raised for the first time in this Court, the Court would have to revisit *Diehr*, overturn settled Federal Circuit precedent, and disapprove the standards by which the PTO has reviewed and issued tens of thousands of patents.

Petitioner seems intent on obscuring from the Court just how radical its position is. By clinging to *Flook* as if it had been left untouched by *Diehr*, failing even to cite the principal Federal Circuit decisions, and ignoring the PTO's *Guide-*

lines, petitioner has chosen to mount a sneak attack on the governing law. But if petitioner were to obtain a decision from this Court questioning the validity of the '658 patent on the ground that it claims non-patentable subject matter, 25 years of consistently applied patent law would come undone.

1. Vacatur Would Call Into Question Thousands Of Issued Patents

"Since this Court decided *Diehr* almost 25 years ago, PTO has generally followed the Federal Circuit's understanding that *Diehr* substantially limited *Flook*, and has issued numerous patents based on that understanding—including patents on medical diagnostic methods, other types of diagnostic and testing procedures, and computer-related processes." U.S. Cert. Br. 14. If this Court were to accept petitioner's invitation and change the law of subject matter patentability, the validity of some or all of those patents would be thrown into doubt. "A decision overturning PTO's approach could call into question a substantial number of patent claims and undermine the settled expectations of numerous participants in technology-based industries." *Ibid.*; *cf. Warner-Jenkinson Co.* v. *Hilton Davis Chem. Co.*, 520 U.S. 17, 32 n.6 (1997) ("To change so substantially the rules of the game now could very well subvert the various balances the PTO sought to strike when issuing the numerous patents which have not yet expired and which would be affected by our decision").[23]

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[23] While petitioner seeks to minimize the impact of a decision in its favor, its *amici* are more straightforward. They recognize that such a decision would further their agenda of abolishing all past, present, and future patents on business methods, software, gene sequences, or medical procedures. *E.g.*, CCIA Br. 2, 6; Financial Services Industry Br. 7-8, 14-17; Affymetrix, Inc. Br. 3-4, 15-16; AARP Br. 2, 9. The wholesale challenge to *State Street* and its progeny mounted by these *amici* should await resolution in

1. A decision questioning the validity of claim 13 of the '658 patent would especially call into question hundreds or thousands of patents on medical diagnostic methods, which frequently recite the sequential steps of assaying (or determining) the amount of a particular substance of the body and correlating the determined amount with a disease. Claim 1 of U.S. Patent No. 6,811,993, for example, claims a three-step diagnostic method of "determining the level of [Protein Kinase C] activity in monocytes of the subject; optionally comparing the level of PKC activity in monocytes of the subject with a standard; and correlating the level of PKC activity with the extent, stage, or severity of the cardiovascular complication of diabetes." Because many diseases are indicated by "markers"—proteins, enzymes, amino acids, or other substances that change (in quantity or behavior) in the presence of the disease—patents on useful diagnostic processes that employ such markers are in fact common. *See* U.S. Patent Nos. 6,461,831 (Background and Written Description) (discussion of this issue in the context of Alzheimer's disease); 6,929,918 (Background and Written Description) (same in the context of prostate cancer).[24]

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a case in which the issue is actually presented by a party. *See Bell* v. *Wolfish*, 441 U.S. 520, 531-32 n.13 (1979).

[24] Although petitioner maintains (Br. 19) that "[c]orrelations are elemental tools of all science, and as such are free to all and patentable by none," a search of the PTO's database indicates that approximately 20,000 patents have issued since 1976 with "correlate" (or a variant thereof) as a claim limitation. The government clearly does not share petitioner's view that correlations are *per se* unpatentable. *See also, e.g.*, U.S. Patent Nos. 6,004,528 (Claim 10) ("method for aiding in the diagnosis of cancer"); 6,962,793 (Claim 1) ("method for diagnosing Alzheimer's disease"); U.S. Patent No. 6,979,533 (Claim 1) ("method for detecting receptivity of the endometrium of a mammal to embryo implantation"); U.S. Patent No. 4,836,218 (Claim 1) (method for detecting temporomandibular joint disorders). *Amicus* ACLA expresses concern (Br.

The havoc caused by a decision questioning the validity of the '658 patent would extend far beyond the realm of medical diagnoses to every patented invention that incorporates a natural relationship (including most drugs, many medical devices, and a host of computer software and hardware applications). For example, on petitioner's theory Bell's process for communicating information over the telephone would have been unpatentable, because it was merely a practical application of the natural phenomenon that electricity can be used to propagate sound waves over a wire. *But see* note 19, *supra*. And pharmaceutical companies could not patent methods of treating conditions such as depression, Alzheimer's, or heart disease with drugs, since they have merely discovered that certain chemicals interact with the human body in ways directed by chemistry and patented practical applications of such discovered interactions. *Cf. Diehr*, 450 U.S. at 189 n.12 ("To accept the analysis proffered by the petitioner would, if carried to its extreme, make all inventions unpatentable because all inventions can be reduced to underlying principles of nature which, once known, make their implementation obvious").

2. The PTO, and the Federal Circuit, have implemented *Diehr* with a workable set of principles of subject matter eligibility that have guided the issuance and review of patents for the past quarter-century. If those standards are flawed such that they ought to be changed, petitioner and its *amici* have at least three avenues of redress.

First, the PTO itself has invited public comment on the standards of subject matter patentability. 70 Fed. Reg. at 75,452; *see Warner-Jenkinson*, 520 U.S. at 33-34 (noting the

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11-13) that a method of diagnosing prostate cancer using antibody assays could be patented. In fact, numerous patents have issued on such diagnostic methods. In addition to Claim 7 of the '918 patent cited in the text above, *see, e.g.*, U.S. Patent No. 6,482,599 (Claim 35).

"primacy of the PTO in ensuring that the claims allowed cover only subject matter that is properly patentable"). Its final guidance, which presumably will be entitled to deference under *Chevron U.S.A. Inc.* v. *Natural Resources Defense Council, Inc.*, 467 U.S. 837, 842-45 (1984), could materially assist in this Court's ultimate review of the issue.

Second, Congress can always step in to change the Patent Act. Indeed, a comprehensive patent reform bill is pending at this moment. *See* "Patent Reform Act of 2005," H.R. 2795, 109th Cong., 1st Sess. (introduced June 8, 2005); *cf. Warner-Jenkinson*, 520 U.S. at 28 ("Congress can legislate the doctrine of equivalents out of existence any time it chooses"). Its decision for the past quarter-century not to override *Diehr* suggests an acceptance of it. *See J.E.M. Ag Supply, Inc.* v. *Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 145-46 (2001) ("As in *Chakrabarty*, we decline to narrow the reach of § 101 where Congress has given us no indication that it intends this result"). This is especially so here, where Congress in the interim has responded to complaints about the patentability of other types of inventions not by restricting patentable subject matter, but by limiting remedies or adding defenses for those inventions. *See* 35 U.S.C. § 287(c) (restricting remedies for surgical procedure patents); 35 U.S.C. § 273(a)(3) (adding prior user defense against business method patents).

And third, the Federal Circuit, established by Congress as the expert court in the patent area, should at least be given the first opportunity to consider these issues. *See Warner-Jenkinson*, 520 U.S. at 40 (noting the Federal Circuit's "sound judgment" in the patent area of its "special expertise").

Petitioner wants to bypass all of these avenues and asks this Court to rule, in the first instance and without the benefit of a full record, that an issued patent, imbued with the statutory presumption of validity, is invalid for failing to claim

patentable subject matter notwithstanding the fact that claim 13 passes all extant requirements for subject matter eligibility. As the Solicitor General has explained, "if this Court were to consider reevaluating almost a quarter-century of administrative practice and lower court jurisprudence, it should do so based on a full record in a case where the issue was properly raised, litigated, and decided below." U.S. Cert. Br. 19. This is not that case.

2. Affirmance (Or Dismissal) Would Have No Adverse Consequences In The Context Of This Case

Petitioner and its *amici* predict dire consequences for public health if the '658 patent stands, going so far as to assert that a decision for respondents would "depriv[e] patients of needed medical services." Pet. Br. 30. At best, these are policy arguments better addressed to the political branches; at worst, they are nothing but scare tactics.

Petitioner is a for-profit company that is seeking to maximize its revenue by avoiding the royalties due respondents under the licensing agreement that petitioner previously entered into. There is not a shred of evidence in the record that petitioner's payment of royalties to respondents, or the ultimate cost of the homocysteine assays performed by petitioner, have ever affected a single doctor's treatment decision. There is absolutely no evidence that, if the judgment below were affirmed (or the writ dismissed), any patient's care, or the cost of that care, would change in any way.[25]

Patented inventions are common in the field of medicine. In addition to diagnostic methods, a physician may employ

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[25] Nor is there any evidence that any doctor will be held liable for patent infringement. As respondents explained in their brief in opposition (at 9), and petitioner has not contested, "[n]ot a single physician has been enjoined, sued or even threatened with suit, and none will be."

diagnostic machinery (such as an MRI machine), medical devices (such as implants or prosthetics), and of course a wide range of pharmaceuticals, all of which may be covered by one or more patents. For this reason, AARP's assertion (Br. 9) that claim 13 "would prohibit physicians from practicing good medicine without a patent license" proves far too much. "Good medicine" may in fact require physicians to practice patented inventions on a daily basis—by engaging in patented diagnostic methods, by using patented devices, or by prescribing patented pharmaceuticals. Although the patent regime may increase (or decrease) the cost of patient care, Congress has made the policy judgment that the benefits of increased innovation provided by the patent system justify any distortions that patents might introduce into the healthcare delivery system.

Indeed, this case proves the soundness of Congress's policy judgment: The patent system helped motivate these Inventors and their universities and agents to conceive of, develop and commercialize an invention that has saved thousands of lives and millions of dollars in health care costs by allowing for prompt and accurate diagnoses of a serious but easily treated condition. *Cf. Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722, 739 (2002) ("Fundamental alterations in these rules risk destroying the legitimate expectations of inventors in their property"). Indeed, over ten million homocysteine assays are now performed each year to detect cobalamin and folate deficiencies.

As Justice Breyer has recognized, this area of the law is a particularly thorny one. Breyer, *supra*, 28 J. L. Med. & Ethics at 27 ("Should it matter if the more apt description of the scientist's work is the 'discovery' of how a portion of the body functions, rather than the 'invention' of how to use a part of that body to perform a useful, say, diagnostic task? This latter question will sometimes seem unanswerable."). For now, the PTO and the Federal Circuit have found *Diehr* a workable guide, and Congress has not seen fit to provide oth-

erwise. If the law is to be changed, it should be in a case in which the issues are pleaded, litigated, and decided at all levels, with full input from all potentially affected constituencies—*not* in this case, where the question of subject matter patentability has been raised by petitioner only at the last stage of the proceedings, and on a spare if not empty record.

CONCLUSION

The judgment of the court of appeals should be affirmed. In the alternative, the writ of certiorari should be dismissed.

Respectfully submitted.

MARK A. LEMLEY
KEKER & VAN NEST LLP
710 Sansome Street
San Francisco, CA 94111
(415) 391-5400

GLENN K. BEATON
Counsel of Record
GIBSON, DUNN & CRUTCHER LLP
1801 California Street
Denver, Colorado 80202
(303) 298-5700

MIGUEL A. ESTRADA
MARK A. PERRY
JEFFREY A. WADSWORTH
GIBSON, DUNN & CRUTCHER LLP
1050 Connecticut Avenue, N.W.
Washington, D.C. 20036-5306
(202) 955-8500

Counsel for Respondents

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Title 35 U.S.C. § 100 provides in pertinent part:

§ 100. Definitions

When used in this title unless the context otherwise indicates—

(a) The term "invention" means invention or discovery.

(b) The term "process" means process, art or method, and includes a new use of a known process, machine, manufacture, composition of matter, or material.

* * * *

Title 35 U.S.C. § 102 provides in pertinent part:

§ 102. Conditions for patentability; novelty and loss of right to patent

A person shall be entitled to a patent unless—

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or

* * * *

(f) he did not himself invent the subject matter sought to be patented[.]

* * * *

Title 35 U.S.C. § 103 provides in pertinent part:

§ 103. Conditions for patentability; non-obvious subject matter

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

* * * *

Title 35 U.S.C. § 282 provides in pertinent part:

§ 282. Presumption of validity; defenses

A patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims * * *. The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity.

The following shall be defenses in any action involving the validity or infringement of a patent and shall be pleaded:

* * * *

(2) Invalidity of the patent or any claim in suit on any ground specified in part II of this title [§§ 100 *et seq.*] as a condition for patentability,

(3) Invalidity of the patent or any claim in suit for failure to comply with any requirement of sections 112 or 251 of this title, [or]

(4) Any other fact or act made a defense by this title.

* * * *

Federal Rule of Civil Procedure 8 provides in pertinent part:

Rule 8. General Rules of Pleading

* * * *

(c) Affirmative Defenses. In pleading to a preceding pleading, a party shall set forth affirmatively accord and satisfaction, arbitration and award, assumption of risk, contributory negligence, discharge in bankruptcy, duress, estoppel, failure of consideration, fraud, illegality, injury by fellow servant, laches, license, payment, release, res judicata, statute of frauds, statute of limitations, waiver, and any other matter constituting an avoidance or affirmative defense. When a party has mistakenly designated a defense as a counterclaim or a counterclaim as a defense, the court on terms, if justice so requires, shall treat the pleading as if there had been a proper designation.

* * * *

Patent Act of 1870, ch. 230, § 61, 16 Stat. 198, 208 provides in pertinent part:

Sec. 61. *And be it further enacted,* That in any action for infringement the defendant may plead the general issue, and having given notice in writing to the plaintiff or his attorney, thirty days before, may prove on trial any one or more of the following special matters: —

First. That for the purpose of deceiving the public the description and specification filed by the patentee in the patent office was made to contain less than the whole truth relative to his invention or discovery, or more than is necessary to produce the desired effect; or,

Second. That he had surreptitiously or unjustly obtained the patent for that which was in fact invented by another,

who was using reasonable diligence in adapting and perfecting the same; or,

Third. That it had been patented or described in some printed publication prior to his supposed invention or discovery thereof; or,

Fourth. That he was not the original and first inventor or discovered of any material and substantial part of the thing patented; or,

Fifth. That it had been in public use or on sale in this country, for more than two years before his application for a patent, or had been abandoned to the public.

* * * *

* * * *

The *Official Gazette of the United States Patent and Trademark Office*, Vol. 1300, No. 4, pp. 142 *ff.* (November 22, 2005), provides in pertinent part:

Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility

* * * *

The principal objective of these guidelines is to assist examiners in determining, on a case-by-case basis, whether a claimed invention falls within a judicial exception to statutory subject matter (i.e., is nothing more than an abstract idea, law of nature, or natural phenomenon), or whether it is a practical application of a judicial exception to statutory subject matter. The guidelines explain that a practical application of a 35 U.S.C. § 101 judicial exception is claimed if the claimed invention physically transforms an article or physical object to a different state or thing, or if the claimed invention otherwise produces a useful, concrete, and tangible result.

I. INTRODUCTION

These Examination Guidelines ("Guidelines") are based on the USPTO's current understanding of the law and are believed to be fully consistent with binding precedent of the Supreme Court, the Federal Circuit and the Federal Circuit's predecessor courts.

These Guidelines do not constitute substantive rulemaking and hence do not have the force and effect of law. These Guidelines have been designed to assist USPTO personnel in analyzing claimed subject matter for compliance with substantive law. Rejections will be based upon the substantive law and it is these rejections which are appealable. Conse-

quently, any failure by USPTO personnel to follow the Guidelines is neither appealable nor petitionable.

The Guidelines set forth the procedures USPTO personnel will follow when examining applications. USPTO personnel are to rely on these Guidelines in the event of any inconsistent treatment of issues between these Guidelines and any earlier provided guidance from the USPTO.

* * * *

Annex I which appears at the end of this section includes a flow chart of the process USPTO personnel should follow.

* * * *

IV. DETERMINE WHETHER THE CLAIMED INVENTION COMPLIES WITH THE SUBJECT MATTER ELIGIBILITY REQUIREMENT OF 35 U.S.C. § 101

A. Consider the Breadth of 35 U.S.C. § 101 Under Controlling Law

Section 101 of title 35, United States Code, provides:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

As the Supreme Court held, Congress chose the expansive language of 35 U.S.C. § 101 so as to include "anything under the sun that is made by man." *Diamond v. Chakrabarty*, 447 U.S. 303, 308-09, 206 USPQ 193, 197 (1980). In *Chakrabarty*, 447 U.S. at 308-309, 206 USPQ at 197, the court stated:

> In choosing such expansive terms as "manufacture" and "composition of matter," modified by the

comprehensive "any," Congress plainly contemplated that the patent laws would be given wide scope. The relevant legislative history also supports a broad construction. The Patent Act of 1793, authored by Thomas Jefferson, defined statutory subject matter as "any new and useful art, machine, manufacture, or composition of matter, or any new or useful improvement [thereof]." Act of Feb. 21, 1793, ch. 11, § 1, 1 Stat. 318. The Act embodied Jefferson's philosophy that "ingenuity should receive a liberal encouragement." V Writings of Thomas Jefferson, at 75-76. See *Graham v. John Deere Co.*, 383 U.S. 1, 7-10 (148 USPQ 459, 462-464) (1966). Subsequent patent statutes in 1836, 1870, and 1874 employed this same broad language. In 1952, when the patent laws were recodified, Congress replaced the word "art" with "process," but otherwise left Jefferson's language intact. The Committee Reports accompanying the 1952 Act inform us that Congress intended statutory subject matter to "include anything under the sun that is made by man." S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952); H.R. Rep. No. 1923, 82d Cong., 2d Sess., 6 (1952). [Footnote omitted]

This perspective has been embraced by the Federal Circuit:

> The plain and unambiguous meaning of section 101 is that any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may be patented if it meets the requirements for patentability set forth in Title 35, such as those found in sections 102, 103, and 112. The use of the expansive term "any" in section 101 represents Congress's intent not to place any restrictions on the subject matter for which a patent may be obtained beyond those specifically

> recited in section 101 and the other parts of Title 35 . . . Thus, it is improper to read into section 101 limitations as to the subject matter that may be patented where the legislative history does not indicate that Congress clearly intended such limitations.

[*In re*] *Alappat*, 33 F.3d [1526,] 1542, 31 USPQ2d [1545,] 1556 [(Fed. Cir. 1994) (en banc)].

35 U.S.C. § 101 defines four categories of inventions that Congress deemed to be the appropriate subject matter of a patent: processes, machines, manufactures and compositions of matter. The latter three categories define "things" or "products" while the first category defines "actions" (i.e., inventions that consist of a series of steps or acts to be performed). See 35 U.S.C. 100(b) ("The term 'process' means process, art, or method, and includes a new use of a known process, machine, manufacture, composition of matter, or material.").

Federal courts have held that 35 U.S.C. § 101 does have certain limits. First, the phrase "anything under the sun that is made by man" is limited by the text of 35 U.S.C. § 101, meaning that one may only patent something that is a machine, manufacture, composition of matter or a process. *See, e.g., Alappat*, 33 F.3d at 1542, 31 USPQ2d at 1556; *In re Warmerdam*, 33 F.3d 1354, 1358, 31 USPQ2d 1754, 1757 (Fed. Cir. 1994). Second, 35 U.S.C. § 101 requires that the subject matter sought to be patented be a "useful" invention. Accordingly, a complete definition of the scope of 35 U.S.C. § 101, reflecting Congressional intent, is that any new and useful process, machine, manufacture or composition of matter under the sun that is made by man is the proper subject matter of a patent.

The subject matter courts have found to be outside of, or exceptions to, the four statutory categories of invention is limited to abstract ideas, laws of nature and natural phenomena. While this is easily stated, determining whether an ap-

plicant is seeking to patent an abstract idea, a law of nature or a natural phenomenon has proven to be challenging. These three exclusions recognize that subject matter that is not a *practical application or use* of an idea, a law of nature or a natural phenomenon is not patentable. *See, e.g., Rubber-Tip Pencil Co. v. Howard*, 87 U.S. (20 Wall.) 498, 507 (1874) ("idea of itself is not patentable, but a new device by which it may be made practically useful is"); *Mackay Radio & Telegraph Co. v. Radio Corp. of America*, 306 U.S. 86, 94, 40 USPQ 199, 202 (1939) ("While a scientific truth, or the mathematical expression of it, is not patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be."); *Warmerdam*, 33 F.3d at 1360, 31 USPQ2d at 1759 ("steps of 'locating' a medial axis, and 'creating' a bubble hierarchy . . . describe nothing more than the manipulation of basic mathematical constructs, the paradigmatic 'abstract idea'").

The courts have also held that a claim may not preempt ideas, laws of nature or natural phenomena. The concern over preemption was expressed as early as 1852. *See Le Roy v. Tatham*, 55 U.S. (14 How.) 156, 175 (1852) ("A principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented, as no one can claim in either of them an exclusive right."); *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 132, 76 USPQ 280, 282 (1948) (combination of six species of bacteria held to be non-statutory subject matter). Accordingly, one may not patent every "substantial practical application" of an idea, law of nature or natural phenomena because such a patent "in practical effect be a patent on the [idea, law of nature or natural phenomena] itself." *Gottschalk v. Benson*, 409 U.S. 63, 71-72, 175 USPQ 673, 676 (1972).

B. Determine Whether the Claimed Invention Falls Within An Enumerated Statutory Category

To properly determine whether a claimed invention complies with the statutory invention requirements of 35 U.S.C. § 101, USPTO personnel must first identify whether the claim falls within at least one of the four enumerated categories of patentable subject matter recited in section 101 (process, machine, manufacture or composition of matter).

In many instances it is clear within which of the enumerated categories a claimed invention falls. Even if the characterization of the claimed invention is not clear, this is usually not an issue that will preclude making an accurate and correct assessment with respect to the section 101 analysis. The scope of 35 U.S.C. § 101 is the same regardless of the form or category of invention in which a particular claim is drafted. *AT&T* [*Corp. v. Excel Communications, Inc.*], 172 F.3d [1352,] 1357, 50 USPQ2d [1447,] 1451 [(Fed. Cir. 1999)]. *See also State Street* [*Bank & Trust Co. v. Signature Financial Group, Inc.*], 149 F.3d [1368,] 1375, 47 USPQ2d [1596,] 1602 [(Fed. Cir. 1998),] wherein the Federal Circuit explained

> The question of whether a claim encompasses statutory subject matter should not focus on *which* of the four categories of subject matter a claim is directed to—process, machine, manufacture, or composition of matter—[provided the subject matter falls into at least one category of statutory subject matter] but rather on the essential characteristics of the subject matter, in particular, its practical utility.

For example, a claimed invention may be a combination of devices that appear to be directed to a machine and one or more steps of the functions performed by the machine. Such instances of mixed attributes, although potentially confusing as to which category of patentable subject matter it belongs in, does not affect the analysis to be performed by the exam-

iner. Note that an apparatus claim with process steps is not classified as a "hybrid" claim; instead, it is simply an apparatus claim including functional limitations. *See, e.g., R.A.C.C. Indus. v. Stun-Tech, Inc.*, 178 F.3d 1309 (Fed. Cir. 1998) (unpublished).

The burden is on the USPTO to set forth a *prima facie* case of unpatentability. Therefore if the examiner determines that it is more likely than not that the claimed subject matter falls outside all of the statutory categories, the examiner must provide an explanation. For example, a claim reciting only a musical composition, literary work, compilation of data, or legal document (e.g., an insurance policy) *per se* does not appear to be a process, machine, manufacture, or composition of matter. If the examiner can establish a *prima facie* case that a claim does not fall into a statutory category, that does not preclude complete examination of the application for satisfaction of all other conditions of patentability. The examiner must further continue with the statutory subject matter analysis as set forth below. Also, the examiner must still examine the claims for compliance with 35 U.S.C. §§ 102, 103, and 112.

If the invention as set forth in the written description is statutory, but the claims define subject matter that is not, the deficiency can be corrected by an appropriate amendment of the claims. In such a case, USPTO personnel should reject the claims drawn to nonstatutory subject matter under 35 U.S.C. § 101, but identify the features of the invention that would render the claimed subject matter statutory if recited in the claim.

C. Determine Whether the Claimed Invention Falls Within § 101 Judicial Exceptions—Laws of Nature, Natural Phenomena and Abstract Ideas

Determining whether the claim falls within one of the four enumerated categories of patentable subject matter recited in 35 U.S.C. § 101 (process, machine, manufacture or composition of matter) does not end the analysis because claims directed to nothing more than abstract ideas (such as mathematical algorithms), natural phenomena, and laws of nature are not eligible and therefore are excluded from patent protection. [*Diamond v.*] *Diehr*, 450 U.S. [175,] 185, 209 USPQ [1,] 7 [(1981)]; accord, e.g., *Chakrabarty*, 447 U.S. at 309, 206 USPQ at 197; *Parker v. Flook*, 437 U.S. 584, 589, 198 USPQ 193, 197 (1978); *Benson*, 409 U.S. at 67-68 , 175 USPQ at 675; *Funk*, 333 U.S. at 130, 76 USPQ at 281. "A principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented, as no one can claim in either of them an exclusive right." *Le Roy*, 55 U.S. (14 How.) at 175. Instead, such "manifestations of laws of nature" are "part of the storehouse of knowledge," "free to all men and reserved exclusively to none." *Funk*, 333 U.S. at 130, 76 USPQ at 281.

Thus, "a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter" under Section 101. *Chakrabarty*, 447 U.S. at 309, 206 USPQ at 197. "Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity." *Ibid.* Nor can one patent "a novel and useful mathematical formula," *Flook*, 437 U.S. at 585, 198 USPQ at 195; electromagnetism or steam power, *O'Reilly v. Morse*, 56 U.S. (15 How.) 62, 113-114 (1853); or "[t]he qualities of * * * bacteria, * * * the heat of the sun, electricity, or the qualities of metals," *Funk*, 333 U.S. at 130, 76 USPQ at 281; see *Le Roy*, 55 U.S. (14 How.) at 175.

While abstract ideas, natural phenomena, and laws of nature are not eligible for patenting, methods and products employing abstract ideas, natural phenomena, and laws of nature to perform a real-world function may well be. In evaluating whether a claim meets the requirements of section 101, the claim must be considered as a whole to determine whether it is for a particular *application* of an abstract idea, natural phenomenon, or law of nature, rather than for the abstract idea, natural phenomenon, or law of nature itself.

1. Determine Whether the Claimed Invention Covers Either a § 101 Judicial Exception or a Practical Application of a § 101 Judicial Exception

An examiner must ascertain the scope of the claim to determine whether it covers either a § 101 judicial exception or a practical application of a § 101 judicial exception. The conclusion that a particular claim *includes* a § 101 judicial exception does not end the inquiry because "[i]t is now commonplace that an *application* of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection." *Diehr*, 450 U.S. at 187, 209 USPQ at 8 (emphasis in original); accord *Flook*, 437 U.S. at 590, 198 USPQ at 197; *Benson*, 409 U.S. at 67, 175 USPQ at 675. Thus, "[w]hile a scientific truth, or the mathematical expression of it, is not a patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be." *Diehr*, 450 U.S. at 188, 209 USPQ at 8-9 (quoting *Mackay*, 306 U.S. at 94); see also *Corning v. Burden*, 56 U.S. (15 How.) 252, 268, 14 L.Ed. 683 (1854) ("It is for the discovery or invention of some practical method or means of producing a beneficial result or effect, that a patent is granted . . .").

2. Determine Whether the Claimed Invention is a Practical Application of an Abstract Idea, Law of Nature, or Natural Phenomenon (§ 101 Judicial Exceptions)

For claims including such excluded subject matter to be eligible, the claim must be for a *practical application* of the abstract idea, law of nature, or natural phenomenon. *Diehr*, 450 U.S. at 187, 209 USPQ at 8 ("*application* of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection."); *Benson*, 409 U.S. at 71, 175 USPQ at 676 (rejecting formula claim because it "has no substantial practical application").

To satisfy section 101 requirements, the claim must be for a practical application of the § 101 judicial exception, which can be identified in various ways:

- The claimed invention "transforms" an article or physical object to a different state or thing.
- The claimed invention otherwise produces a useful, concrete and tangible result, based on the factors discussed below.

a. Practical Application by Physical Transformation

The examiner first shall review the claim and determine if it provides a transformation or reduction of an article to a different state or thing. If the examiner finds such a transformation or reduction, the examiner shall end the inquiry and find that the claim meets the statutory requirement of 35 U.S.C. § 101. If the examiner does not find such a transformation or reduction, the examiner has not determined as a final matter that the claim is non-statutory. The examiner must proceed in further inquiry.

b. Practical Application That Produces a Useful, Concrete, and Tangible Result

For eligibility analysis, physical transformation "is not an invariable requirement, but merely one example of how a mathematical algorithm [or law of nature] may bring about a useful application." *AT&T*, 172 F.3d at 1358-59, 50 USPQ2d at 1452. If the examiner determines that the claim does not entail the transformation of an article, then the examiner shall review the claim to determine if the claim provides a practical application that *produces* a useful, tangible and concrete *result*. In determining whether the claim is for a "practical application," the focus is not on whether the steps taken to achieve a particular result are useful, tangible and concrete, but rather that *the final result achieved* by the claimed invention is "useful, tangible and concrete." The claim must be examined to see if it includes anything more than a § 101 judicial exception. If the claim is directed to a practical application of the § 101 judicial exception producing a result tied to the physical world that does not preempt the judicial exception, then the claim meets the statutory requirement of 35 U.S.C. § 101. If the examiner does not find such a practical application, the examiner has determined that the claim is nonstatutory.

In determining whether a claim provides a practical application that produces a useful, tangible, and concrete result, the examiner should consider and weigh the following factors:

(1) "USEFUL RESULT"

For an invention to be "useful" it must satisfy the utility requirement of section 101. The USPTO's official interpretation of the utility requirement provides that the utility of an invention has to be (i) specific, (ii) substantial *and* (iii) credible. MPEP § 2107 and [*In re*] *Fisher*, 421 F.3d [1365,] ___, 76 USPQ2d [1225,] 1230 [(Fed. Cir. 2005)] (citing the Util-

ity Guidelines with approval for interpretation of "specific" and "substantial"). In addition, when the examiner has reason to believe that the claim is not for a practical application that produces a useful result, the claim should be rejected, thus requiring the applicant to distinguish the claim from the three § 101 judicial exceptions to patentable subject matter by specifically reciting in the claim the practical application. In such cases, statements in the specification describing a practical application may not be sufficient to satisfy the requirements for section 101 with respect to the claimed invention. Likewise, a claim that can be read so broadly as to include statutory and nonstatutory subject matter must be amended to limit the claim to a practical application. In other words, if the specification discloses a practical application of a § 101 judicial exception, but the claim is broader than the disclosure such that it does not require a practical application, then the claim must be rejected.

(2) "TANGIBLE RESULT"

The tangible requirement does not necessarily mean that a claim must either be tied to a particular machine or apparatus or must operate to change articles or materials to a different state or thing. However, the tangible requirement does require that the claim must recite more than a § 101 judicial exception, in that the process claim must set forth a practical application of that § 101 judicial exception to produce a real-world result. *Benson*, 409 U.S. at 71-72, 175 USPQ at 676-77 (invention ineligible because had "no substantial practical application."). "[A]n *application* of a law of nature or mathematical formula to a . . . process may well be deserving of patent protection." *Diehr*, 450 U.S. at 187, 209 USPQ at 8 (emphasis added); *see also Corning*, 56 U.S. (15 How.) at 268, 14 L.Ed. 683 ("It is for the discovery or invention of some practical method or means of producing a beneficial result or effect, that a patent is granted . . ."). In other words, the opposite meaning of "tangible" is "abstract."

(3) "CONCRETE RESULT"

Another consideration is whether the invention produces a "concrete" result. Usually, this question arises when a result cannot be assured. In other words, the process must have a result that can be substantially repeatable or the process must substantially produce the same result again. *In re Swartz*, 232 F.3d 862, 864, 56 USPQ2d 1703, 1704 (Fed. Cir. 2000) (where asserted result produced by the claimed invention is "irreproducible" claim should be rejected under section 101). The opposite of "concrete" is unrepeatable or unpredictable. Resolving this question is dependent on the level of skill in the art. For example, if the claimed invention is for a process which requires a particular skill, to determine whether that process is substantially repeatable will necessarily require a determination of the level of skill of the ordinary artisan in that field. An appropriate rejection under 35 U.S.C. § 101 should be accompanied by a lack of enablement rejection under 35 U.S.C. § 112, paragraph 1, where the invention cannot operate as intended without undue experimentation. *See infra.*

3. Determine Whether the Claimed Invention Preempts an Abstract Idea, Law of Nature, or Natural Phenomenon (§ 101 Judicial Exceptions)

Even when a claim applies a mathematical formula, for example, as part of a seemingly patentable process, the examiner must ensure that it does not in reality "seek[] patent protection for that formula in the abstract." *Diehr*, 450 U.S. at 191, 209 USPQ at 10. "Phenomena of nature, though just discovered, mental processes, abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." *Benson*, 409 U.S. at 67, 175 USPQ at 675. One may not patent a process that comprises every "substantial practical application" of an abstract idea, because such a patent "in practical effect would be a patent on the [abstract idea] itself." *Benson*, 409 U.S. at 71-72, 175

USPQ at 676; *cf. Diehr*, 450 U.S. at 187, 209 USPQ at 8 (stressing that the patent applicants in that case did "not seek to pre-empt the use of [an] equation," but instead sought only to "foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process"). "To hold otherwise would allow a competent draftsman to evade the recognized limitations on the type of subject matter eligible for patent protection." *Diehr*, 450 U.S. at 192, 209 USPQ at 10. Thus, a claim that recites a computer that solely calculates a mathematical formula (*see Benson*) or a computer disk that solely stores a mathematical formula is not directed to the type of subject matter eligible for patent protection. If an examiner determines that the claimed invention preempts a § 101 judicial exception, the examiner must identify the abstraction, law of nature, or natural phenomenon and explain why the claim covers every substantial practical application thereof.

D. Establish on the Record a Prima Facie Case

The examiner should review the totality of the evidence (e.g., the specification, claims, relevant prior art) before reaching a conclusion with regard to whether the claimed invention sets forth patent eligible subject matter. The examiner must weigh the determinations made above to reach a conclusion as to whether it is more likely than not that the claimed invention as a whole either falls outside of one of the enumerated statutory classes or within one of the exceptions to statutory subject matter. "The examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). If the record as a whole suggests that it is more likely than not that the claimed invention would be considered a practical application of an abstract idea, natural phenomenon, or law of nature, the examiner should not reject the claim.

After the examiner identifies and explains in the record the basis for why a claim is for an abstract idea with no practical application, then the burden shifts to the applicant to either amend the claim or make a showing of why the claim is eligible for patent protection. *See, e.g., In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995); *see generally* MPEP § 2107 (Utility Guidelines).

* * * * *

Date: 10/26/05

/s/
JOHN J. DOLL
Commissioner for Patents

ANNEX I

Flowchart for Subject Matter Eligibility

* * * *

DETERMINE WHETHER THE CLAIMED INVENTION COMPLIES WITH THE SUBJECT MATTER ELIGIBILITY REQUIREMENT OF 35 U.S.C. § 101

- Does the Claimed Invention Fall Within an Enumerated Statutory Category?
- Does the Claimed Invention Fall Within a § 101 Judicial Exception—Law of Nature, Natural Phenomena or Abstract Idea?
    - Does the Claimed Invention Cover a § 101 Judicial Exception, or a Practical Application of a § 101 Judicial Exception?
        - Practical Application by Physical Transformation?
        - Practical Application That Produces a Useful (35 U.S.C. § 101 utility), Tangible, and Concrete Result?
    - Does the Claimed Invention Preempt an Abstract Idea, Law of Nature, or Natural Phenomenon (§ 101 Judicial Exception)?
- Establish on the Record a Prima Facie Case

* * * *

ANNEX III

Improper Tests For Subject Matter Eligibility

As set forth in the patent eligible subject matter interim guidelines, a practical application of a 35 U.S.C. § 101 judicial exception is claimed if the claimed invention physically transforms an article or physical state to a different state or thing, or if the claimed invention otherwise produces a useful, concrete, and tangible result. Therefore the following tests are ***not*** to be applied by examiners in determining whether the claimed invention is patent eligible subject matter:

(A) "not in the technological arts" test

(B) *Freeman-Walter-Abele* test

(C) mental step or human step tests

(D) the machine implemented test

(E) the *per se* data transformation test.

* * * *

c. (i) The Mental Step Test

If a claimed process is performed by a machine, it is immaterial whether some or all the steps could be carried out by the human mind. As stated in [*In re*] *Musgrave*, 431 F.2d [882,] 893, 167 USPQ [280,] 289-90 [(C.C.P.A. 1970)]: "[W]e cannot agree with the board that these claims (all the steps of which can be carried out by the disclosed apparatus) are directed to non-statutory processes merely because **some or all** [emphasis added] the steps therein can also be carried out in or with the aid of the human mind or because it may be necessary for one performing the processes to think." Therefore, USPTO personnel should no longer rely on the mental step test to determine whether a claimed invention is directed to statutory subject matter. If all the steps of a claimed proc-

ess can be carried out in the human mind, examiners must determine whether the claimed process produces a useful, tangible, and concrete result, i.e., apply the practical application test set forth in *State Street*.

c. (ii) The Human Step Test

It is immaterial whether the process may be performed by some or all steps that are carried out by a human. Claims are not directed to non-statutory processes merely because **some or all** the steps therein can also be carried out in or with the aid of a human or because it may be necessary for one performing the processes to do some or all of the process steps. The inclusion in a patent of a process that may be performed by a person is not fatal to patentability. *Alco Standard Corp. v. Tennessee Valley Authority*, 808 F.2d 1490, 1496, 1 USPQ2d 1337, 1341 (Fed. Cir. 1987) (citing *Diehr*, 450 U.S. at 175); *see e.g. Smith & Nephew, Inc. v. Ethicon, Inc.*, 276 F.3d 1304, 61 USPQ2d 1065 (Fed. Cir. 2001) (method claim where all the steps are carried out by a human). Therefore, USPTO personnel should no longer rely on the human step test to determine whether a claimed invention is directed to statutory subject matter.

* * * *

(33)

No. 04-607

IN THE

Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS (doing business as LabCorp),

Petitioner,

v.

METABOLITE LABORATORIES, INC. and COMPETITIVE TECHNOLOGIES, INC.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

REPLY BRIEF FOR PETITIONER

JONATHAN S. FRANKLIN*
CATHERINE E. STETSON
JESSICA L. ELLSWORTH
HOGAN & HARTSON L.L.P.
555 Thirteenth Street, N.W.
Washington, D.C. 20004
(202) 637-5766

* Counsel of Record

Counsel for Petitioner

WILSON-EPES PRINTING CO., INC. – (202) 789-0096 – WASHINGTON, D. C. 20001

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REPLY BRIEF FOR PETITIONER

Respondents' brief is notable for what it does not contest. Respondents do not contest that, under the Federal Circuit's construction, every doctor who orders a homocysteine test and simply thinks about what the result might signify has infringed Claim 13. They do not contest that this holding has allowed them to monopolize *all* homocysteine testing, whether accomplished via methods existing before the Patent application, methods developed thereafter, or methods yet to be developed. And they do not contest that, if Claim 13 is valid, anyone who discovers a naturally occurring medical correlation could monopolize known and unknown testing methods by similarly drafting a vague "test plus correlate" claim.

Claim 13 involves nothing of any significance beyond the natural correlation it recites. As such, it violates both the proscription against patenting laws of nature or natural phenomena and the requirement under 35 U.S.C. § 112 that a valid claim recite and describe more than just a scientific principle. Respondents' attempts to defend their indefensible patent claim are refuted by the vast and ill-defined breadth of the claim – which recites *no* steps directing anyone to physically transform anything – and by this Court's precedents which hold that an artful draftsperson cannot render a patent valid merely by specifying a broad category of intended use.

The parties and amici have vigorously joined issue on all aspects of the question whether Claim 13 constitutes a prohibited monopoly over a basic scientific relationship rather than a patentable invention. That purely legal question is properly before the Court because it is included within the question on which certiorari was granted – over the same procedural objection respondents now belatedly raise. It is also a component of the Section 112 issues that are concededly before the Court, it was posed below, and it is an important question affecting the public interest that the Court has the inherent authority to consider. The Court should answer that question and reverse the judgment.

ARGUMENT

I. THE COURT CAN AND SHOULD ANSWER THE QUESTION PRESENTED.

There is no dispute that the Court has *jurisdiction* to consider whether Claim 13 seeks to patent a scientific principle. *See City of Canton* v. *Harris*, 489 U.S. 378, 383-384 (1989) ("respondent's contention that the claims made by petitioner here were not made in the same fashion below * * * does not affect our jurisdiction"). And there is no compelling prudential reason not to decide the legal issue on which certiorari was granted. The Court considered the petition carefully for a year, granted certiorari only after having been apprised in detail by the Solicitor General of the procedural objection respondents now belatedly raise, and limited the grant to the one question that LabCorp had made clear included subject matter patentability. As the Court has stated when presented at the merits stage with this kind of non-jurisdictional objection, "[i]n granting certiorari, [the Court] necessarily considered and rejected that contention as a basis for denying review." *United States* v. *Williams*, 504 U.S. 36, 40 (1992).

1. Now that certiorari has been granted, and there is no jurisdictional bar, the Court may consider any issue "fairly included" in the question presented. S. Ct. R. 14.1(a). Subject matter patentability is fairly included within the question presented, and should be decided for that reason alone. *See Vance* v. *Terrazas*, 444 U.S. 252, 258 n.5 (1980) (Court will consider issue necessary for an "intelligent resolution" of question presented); *Rumsfeld* v. *FAIR*, No. 04-1152, slip op. at 6 (U.S. 2006). The Court granted certiorari to decide, *inter alia*, whether Claim 13 "can validly claim a monopoly over a basic scientific relationship used in medical treatment." Pet. i. This "fairly include[s]" the question whether Claim 13 effectively seeks to patent a scientific principle. Not only is that the plain import of the words, but the petition repeatedly cited and relied on *Diamond* v. *Diehr*, 450 U.S. 175 (1981), and its predecessors, including in attacking validity. *See, e.g.*, Pet. 18, 19, 25-26, 27, 29; Pet. Reply 6. And even if

that were not sufficient to apprise the Court and the public of the precise contours of the question, LabCorp's supplemental brief before certiorari expressly stated that Question 3 of the petition *did* include the issue. *See* LabCorp Supp. Br. 5.[1]

Respondents are almost alone in professing not to understand that fact; even amici on their side agree that the question presented includes subject matter patentability. *See* Boston Patent Law Ass'n Br. 2; Perlegen Sciences Br. 3-25; Franklin Pierce Br. 2-30.[2] Respondents' argument that the petition only raised the issue to note a "consequence[ ]" of the Federal Circuit's decision, Resp. Br. 25, ignores reality. The petition stated that "[i]f the Federal Circuit decision is not corrected, CTI and others like it would improperly gain monopolies over basic scientific facts rather than any novel inventions of their own. * * * [T]his Court's precedents are settled that no such claim can be allowed." Pet. 25 (citing cases at Pet. 18). This was – almost verbatim – just what LabCorp had argued in the Federal Circuit. *See* Pet. Br. 14.

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[1] Given that the petition expressly relied on *Diehr* and other subject matter patentability cases, it was not necessary also to specifically cite 35 U.S.C. § 101 in order to present that issue. The Court's "jurisdiction does not depend on citation to book and verse." *Eddings* v. *Oklahoma*, 455 U.S. 104, 113 n.9 (1982). This Court's own invitation order cited *Diehr* but not § 101, yet the Solicitor General clearly understood the question the Court posed.

[2] Splitting hairs, the Solicitor General argues that Question 3 includes only one patentability sub-theory – whether Claim 13 preempts all substantial practical applications of the correlation. U.S. Br. 17. The question, however, asks whether the "patent * * * can validly claim a monopoly over a basic scientific relationship." Pet. i. Neither the question nor the petition is limited to any sub-theory. Tellingly, when the Court asked the Solicitor General in general terms whether Claim 13 is "invalid because one cannot patent 'laws of nature, natural phenomena, and abstract ideas,'" 125 S. Ct. 1413 (citation omitted), the Solicitor General did not limit his response to just one sub-theory. U.S. Cert. Br. 5-7, 11-15.

Respondents now belatedly object to this Court's consideration of the issue. But the very waiver principles on which they rely demonstrate that the Court can and should decide the question presented. Rule 15.2 of this Court "admonishe[s]" respondents "to point out in the brief in opposition and not later, any perceived misstatement made in the petition," and states that "[a]ny objection to consideration of a question presented *based on what occurred in the proceedings below*, if the objection does not go to jurisdiction, may be deemed waived unless called to the Court's attention in the brief in opposition." S. Ct. R. 15.2 (emphasis added). Respondents' brief in opposition failed to object in any way to consideration of subject matter patentability based on what occurred below or otherwise. And they continued to stand mute even *after* the Court specifically identified that issue and LabCorp's supplemental brief resolved any possible doubt that the issue was included within Question 3 – despite having had the same opportunity to file a supplemental brief.

The Court has held that "we do not think that judicial economy is served" by invoking a non-jurisdictional waiver objection "*after* we have granted certiorari and the case has received plenary consideration on the merits." *Oklahoma City v. Tuttle*, 471 U.S. 808, 815-816 (1985) (emphasis in original). That is because the "decision to grant certiorari represents a commitment of scarce judicial resources with a view to deciding the merits of one or more of the questions presented in the petition." *Id. Accord, City of Canton*, 489 U.S. at 384 ("because respondent did not oppose our grant of review at that time based on her contention that these claims were not pressed below, we will not dismiss the writ as improvidently granted"). So too here. The Court granted certiorari on an important legal question on which the parties and amici have fully joined issue. All that is left is to decide it.

2. The Court need go no further to conclude that it can and should decide the threshold issue of subject matter patentability. But the issue cannot be avoided for a further reason: it is a necessary component of the Section 112 questions that

all parties agree are properly before the Court.[3] It is conceded that the petition raises the question whether Claim 13 is invalid for insufficient enablement, disclosure, or description under Section 112, and that this question was expressly raised at all levels below. *See* Resp. Br. 13-18; Pet. App. 16a-18a. Respondents wrongly contend that this issue is "wholly separate" from whether Claim 13 seeks to patent a scientific principle. Resp. Br. 25 (emphasis deleted). In fact, this Court's landmark ruling in *O'Reilly v. Morse*, 56 U.S. (15 How.) 62 (1853), belies that assertion.

Morse originated the rule against patenting laws of nature or natural phenomena. *See* Pet. Br. 19. But the actual holding of *Morse* was that the claim at issue failed to meet the disclosure and enablement requirements currently set forth in 35 U.S.C. § 112.[4] The claim had sought to patent the use of a natural phenomenon – electromagnetism – for printing characters at a distance. The Court held that this claim violated the statutory requirements, now in Section 112, that a patentee "must deliver a written description of his invention or discovery, 'and of the manner and process of making,

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[3] The District Court understood this. In ruling on LabCorp's JMOL motion, the court stated that "whether you really can patent an idea * * * rather than a method" was "part of the argument." J.A. 174. LabCorp explained the same point to the Federal Circuit. *See* Pet. Br. 14. In any event, a party in this Court is not limited to the specific arguments made in support of a claim below. *See Yee v. City of Escondido*, 503 U.S. 519, 534 (1992).

[4] *See, e.g., LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005) (citing *Morse* for § 112 standard); *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 929 n.9 (Fed. Cir. 2004) (same); *In re Hyatt*, 708 F.2d 712, 714 (Fed. Cir. 1983) (*Morse* involved "what used to be known as 'undue breadth,' but has since been appreciated as being * * * based on the first paragraph of § 112"); *Application of De Castelet*, 562 F.2d 1236, 1242 (C.C.P.A. 1977) (*Morse* "principally involv[ed] an issue raisable today under § 112"); *cf. Holland Furniture Co. v. Perkins Glue Co.*, 277 U.S. 245, 257 (1928).

constructing, using, and compounding the same,' in such exact terms as to enable any person skilled in the art * * * to make, construct, compound, and use the same." 56 U.S. at 118 (quoting Patent Act of 1836, ch. 357, § 6, 5 Stat. 117).

As the Court held (*id.* at 119-120):

> [T]his claim can derive no aid from the specification filed. It is outside of it, and the patentee claims beyond it. And if it stands, it must stand simply on the ground that the broad terms abovementioned were a sufficient description, and entitled him to a patent in terms equally broad. In our judgment the act of Congress cannot be so construed.

The claim was thus invalid because Morse "claims what he has not described in the manner required by law." *Id.* at 120.

Just as Morse's claim was invalid under what is now Section 112 because it broadly claimed a natural phenomenon not limited to his actual telegraph invention, Claim 13 is likewise invalid under Section 112 because it broadly claims a natural correlation not limited to the patentees' inventive assay method. That makes sense, for Congress could not have intended for the disclosure and enablement requirements to be met where no patentable "invention" exists in the first place. Pet. Br. 33 n.19. As in *Morse*, to decide the questions concededly presented here the Court must first confront whether Claim 13 seeks to patent a scientific principle.[5]

3. That issue was also passed upon by the District Court, which incorporated the bar against patenting scientific ideas into its claim construction.[6] And the Federal Circuit simply

[5] In *Diehr*, 450 U.S. at 189-191, the Court held that a claim that is anticipated or obvious under Sections 102 and 103 could still involve patentable subject matter. But the Court did not hold the converse, *i.e.*, that a non-patentable claim could satisfy Section 102 or Section 103. Nor, moreover, did the Court discuss Section 112, much less overrule *Morse*.

[6] *See* Pet. Br. 10; J.A. 131 ("[W]hat my ruling was is that you can't patent an idea. You have to patent an act or the test."); J.A.

ignored LabCorp's argument that not adhering to that critical limitation would render the claim invalid under *Diehr*. *See* Pet. Br. 14. But in any event, it has long been settled that "the question whether [an] invention is patentable or not[] is always open to the consideration of the court." *Slawson* v. *Grand St. R.R.*, 107 U.S. 649, 652 (1883); *see Richards* v. *Chase Elevator Co.*, 158 U.S. 299, 301, 302 (1895); *Hill* v. *Wooster*, 132 U.S. 693, 698 (1890); *Hendy* v. *Golden St. & Miners' Iron-Works*, 127 U.S. 370, 375 (1888); U.S. Cert. Br. 16 (Court has "inherent discretion" to consider issue).

This rule was not "abrogated" long ago. Resp. Br. 20. In fact, it was noted only last year that *Slawson* and its progeny "remain good law." *SmithKline Beecham Corp.* v. *Apotex Corp.*, 403 F.3d 1331, 1353 (Fed. Cir. 2005) (Gajarsa, J., concurring). Thus, in *SmithKline* the court decided subject matter patentability even though it had not been raised below. *See id.* at 1342 (rejecting argument on the merits). Respondents' assertion that the 1952 Patent Act overruled this rule *sub silentio* is further belied by the many other cases applying the rule after 1952.[7] The rationale for the rule remains valid: "[t]he centrality of patentable subject matter to the entire scope of patent law suggests that there are times when such inquiries are critical," particularly given the "significant

60 ("'Correlating' * * * must mean more than the simple existence of a relationship between a high level of homocysteine and a deficiency in cobalamin or folate.").

[7] *See id.* at 1353-54 (collecting cases); *Howes* v. *Great Lakes Press Corp.*, 679 F.2d 1023, 1028 (2d Cir. 1982) ("Section 101 deals with the subject matter of patents and, as such, it is 'always open to the consideration of the court.'") (citing *Slawson*); *Borden Co.* v. *Clearfield Cheese Co.*, 369 F.2d 96, 99-100 (3d Cir. 1966) ("It has been clear from an early date, that the court could dismiss a bill because the invention described in the patent was not patentable, even when no defense of invalidity was set up in the answer."); *Barkeij* v. *Lockheed Aircraft Corp.*, 210 F.2d 1, 2 (9th Cir. 1954) ("it is the duty of the court to dismiss a patent infringement suit whenever it affirmatively appears that the patent is invalid").

public policy interest in removing invalid patents from the public arena." *SmithKline*, 403 F.3d at 1353, 1354 (Gajarsa, J., concurring). Nothing in the pleading provisions of 35 U.S.C. § 282 speaks to, much less abrogates, this Court's settled inherent jurisdiction to consider this important legal issue. *See* S. Rep. No. 82-1979, at 9 (1952) (Section 282 did "not materially chang[e] the substance" of prior law); *cf. Salahuddin* v. *Jones*, 992 F.2d 447, 449 (2d Cir. 1993) (non-pleading of affirmative defense "does not deprive a court of the power to dismiss a claim on that ground"); 18 C. Wright, A. Miller, & E. Cooper, *Federal Practice and Procedure* § 4405, at 85-86 & n.8 (2002 & Supp. 2005) (same).[8]

Subject matter patentability is a pure "question of law" that is resolved by the court alone. *Mahn* v. *Harwood*, 112 U.S. 354, 358 (1884). Respondents cite *no* case where any part of that inquiry was held to be a jury issue, and this is not such a case. The invalidity of Claim 13 is apparent based solely on the Patent itself and the Federal Circuit's construction of it.[9]

[8] In any event, § 282 does not require specific pleading of § 101. Section 282(2) provides for pleading of invalidity on any ground "specified in part II of this title as a condition for patentability." 35 U.S.C. § 282(2). The only two grounds in part II of Title 35 specified as "Conditions for patentability" are Sections 102 and 103 – not Section 101. *See J.P. Stevens & Co.* v. *Lex Tex Ltd.*, 747 F.2d 1553, 1561 (Fed. Cir. 1984). And even if § 282(2) could be read, contrary to its text, to embrace other provisions not listed as "conditions for patentability," that would include § 112, which is also in part II. But § 282(3) provides *specifically* for pleading of invalidity under § 112. Section 282(2) thus could not require specific identification of Sections 101, 112 and every other ground in part II, because that would render redundant the part of § 282(3) that specifically identifies § 112. At most, § 282 provides for general notice of an invalidity defense, and for specific pleading of a § 112 defense (which was done here, *see* J.A. 66).

[9] Respondents' citation to *Unitherm Food Sys., Inc.* v. *Swift-Eckrich, Inc.*, 126 S. Ct. 980 (2006), is inapposite because subject matter patentability is not a jury issue for trial. *See Neely* v. *Martin K. Eby Const. Co.*, 386 U.S. 317, 327 (1967) ("issues of law" are "precisely the kind of issues that the losing defendant below may bring to the court of appeals without ever moving for a new trial"). In any event, unlike in *Unitherm*, LabCorp did renew its JMOL motion challenging the sufficiency of the evidence on factual issues that were for the jury. LabCorp argued there was no evidence doctors performed the necessary active step beyond mental recognition of the natural correlation, which the District Court had required to avoid invalidity. *See, e.g.*, LabCorp Renewed Mot. for JMOL 5 ("As interpreted by the Court, the second step of claim 13 must be 'a discrete step in a sequential process.' The Court has held that the second step must be an active step – a mental step is insufficient.") (R. 249). Respondents themselves understood LabCorp to have thereby presented subject matter patentability. *See* Plfs.' Resp. to Def's. Renewed Mot. for JMOL 15-17 (R. 263).

Whether that purely legal issue is considered in connection with the Section 112 arguments that are indisputably before the Court, or on its own, this Court can and should decide it.

II. CLAIM 13 IS INVALID.

It is not surprising that respondents expend so much effort urging the Court not to answer the question presented, because their argument on the merits is so feeble. A straightforward application of this Court's existing precedents compels the conclusion that Claim 13 is invalid.

A. Claim 13 Seeks To Patent A Scientific Principle.

1. LabCorp has shown that Claim 13 is invalid because it involves nothing of significance beyond the recited correlation. Pet. Br. 23-26. Respondents barely respond, asserting in a footnote that "the Court has never held that 'post-solution activity' is a prerequisite to patentability." Resp. Br. 33 n.15. That is not so. "[I]nsignificant post-solution activity will not transform an unpatentable principle into a patentable process." *Diehr*, 450 U.S. at 191-192. The same is necessarily true of the insignificant "pre-solution" activity of ascertaining an input for a correlation. *See Parker* v. *Flook*, 437 U.S. 584, 585 (1978) (invalidating patent despite "initial step which merely measures the present value of [a] variable").

Respondents do not contest that, if Claim 13 is valid, Einstein could have patented his famous equation by drafting a similar test-plus-correlate claim. *See* Pet. Br. 25. Even the PTO has made clear that "a claimed process which consists solely of the steps that one must follow to solve the mathematical representation of $E=mc^2$ is indistinguishable from the law of nature and would 'preempt' the law of nature. A patent cannot be granted on such a process."[10] The only thing that Claim 13 adds to the natural correlation is the empty requirement that the input be ascertained by *any* manner of test.

2. Respondents' principal defense is that the assay, or measuring, step of Claim 13 "[e]ntails" a physical transformation of matter because presently known methods of assaying for total homocysteine involve molecular disruptions. *See* Resp. Br. 33, 34. But what respondents trumpet as the saving virtue of Claim 13 – the generic measuring step – is in fact its worst vice. Claim 13 does not direct anyone how to physically transform anything. Instead, it covers *all* conceivable methods of assaying, whether previously known or yet to be invented. A generic direction to measure a manifestation of nature does not transform the phenomenon into patentable subject matter.

That some or all of these undescribed methods may entail physical transformation does not validate the attempt to patent a natural correlation. For example, the claim invalidated in *Morse* could only be implemented through some form of manufactured machine, but that did not save it. Likewise, it

[10] *Interim Guidelines for* [illegible]*ation of Patent Applications for Patent Subject Matter* [illegible], 1300 Off. Gaz. 142, Anx. V (2005). Thus, these Interim Guidelines do not support respondents. In any event, respondents wrongly assert that the Guidelines would be entitled to deference from this Court. *See* Resp. Br. 28. The PTO follows this Court, not vice versa. *See United States ex rel. Steinmetz* v. *Allen*, 192 U.S. 543, 560 (1904); *see also* 70 Fed. Reg. 75452 (Dec. 20, 2005) (extending comment period on Interim Guidelines to take account of Court's decision in this case).

may well be that all current methods of measuring energy entail physical transformation at the molecular level, but that would not validate a patent on Einstein's correlation between energy and mass. Claims that fully disclose and enable specific processes for physically transforming matter are usually patentable because they create something that did not previously exist in nature, and describe exactly what has been invented and what has not. For example, the Patent at issue *does* describe a transformative process – *the specific assay method recited in Claims 1-12* – and the validity of those claims is unchallenged. But *Claim 13* does not disclose, describe, or enable any such process.[11]

3. Respondents next argue that Claim 13 is valid merely if it produces a "useful, concrete, and tangible result." Resp. Br. 36-38. As support, respondents cite only Federal Circuit cases considering business methods and algorithms bearing no resemblance to Claim 13.[12] But this Court's precedents hold that the utility of a claimed application of a law of nature, while *necessary* to validity, is not *sufficient*. *See* Pet. Br. 30-31. The claims invalidated in *Morse*, *Funk Bros.*, *Benson* and *Flook* all produced useful, concrete, and tangible results, yet that did not suffice.

Indeed, the claim struck down in *Morse* involved one of the most useful concepts ever discovered – using electromagnetism to send information at a distance – which is the basis of all modern telecommunications.[13] And respondents' argu-

[11] The Guidelines upon which respondents mistakenly rely state that a claim is patentable if it "*provides* a transformation" of an article to a different state. Resp. Br. 14a (emphasis added). They do not, however, direct a finding of patentability for claims that nowhere recite or disclose a transformative process.

[12] The Federal Circuit originated the "useful, concrete, and tangible" phrase in the context of a machine claim employing an algorithm. *In re Alappat*, 33 F.3d 1526, 1544 (Fed. Cir. 1994).

[13] The inclusion of the term "discovery" in the statutory definition of "invention," 35 U.S.C. § 100(a), does not help respondents.

ment is virtually identical to the unsuccessful argument of the dissenters in *Morse*. The dissent argued that Morse's overbroad claim should be valid because the concept was "not only 'a new and useful art,' * * * but a most wonderful and astonishing invention, requiring tenfold more ingenuity and patient experiment to perfect it, than the art of printing with types and press, as originally invented." 56 U.S. at 134 (Grier, J., dissenting). According to the dissent, "[i]f the result of this application be a new and useful art, and if the essence of his invention consists in compelling this hitherto useless element to record letters and words, at any distance and in many places at the same moment, how can it be said that the claim is for a principle or an abstraction?" *Id.* at 135.

The Court rejected that argument then, and should do so again now. Respondents' rule would eviscerate the prohibition against patenting laws of nature or natural phenomena, for virtually any such principle worth attempting to patent will have practical utility. *Diehr* did not adopt this radical view, nor did it overrule the more than a century of precedent to the contrary.[14] The saving feature of the claim at issue in *Diehr* was not simply its utility, but rather that it described a new method of physical transformation employed in an industrial process. *See* 450 U.S. at 184 ("That respondents' claims involve the transformation of an article, in this case raw, uncured synthetic rubber, into a different state or thing

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Cf. Resp. Br. 18. As used in the statute, a discovery is a fortuitous invention. *See* Affymetrix Br. 24-25 n.19; Amer. Heart Ass'n Br. 9-10. Laws of nature "are not the kind of 'discoveries' that the statute was enacted to protect." *Flook*, 437 U.S at 593.

[14] Nor did *Diehr* "reject[ ]" or "supersede[ ]" *Flook* in any other material respect. Resp. Br. 37. *Diehr* clarified that, in determining validity, "claims must be considered as a whole." 450 U.S. at 188. Here, when Claim 13 is considered "as a whole," it involves nothing of significance beyond the natural correlation it recites. Unlike in *Diehr*, this is not an instance where "'the whole in some way exceed[s] the sum of its parts.'" *Id.* at 193 n.15 (citation omitted).

cannot be disputed."). Claim 13 describes no such method. Instead, as construed by the Federal Circuit it involves merely the reflexive recognition of a natural correlation accompanied only by the token step of ascertaining the input for that correlation. More is required for a valid patent.

4. Because Claim 13 clearly lacks the criteria laid out in *Morse* and its progeny – it describes no process of physical transformation and involves nothing of significance beyond the natural phenomenon it recites – there is no need to also examine whether Claim 13 substantially preempts practical applications of the correlation. *See* Pet. Br. 28-29. Such preemption would invalidate even a claim that meets other criteria for a patentable invention; but not even respondents contend that a claim is patentable as long as it passes the preemption test. To the contrary, this Court has consistently held that a patent on a law of nature is invalid "regardless of whether the patent is intended to cover all uses of [the law] or only limited uses." *Diehr*, 450 U.S. at 192 n.14.

But the vast breadth of Claim 13 creates a prohibited preemptive effect, even more so than the claim invalidated in *Benson*. Claim 13, as construed below, covers *every* homocysteine test by every method – whether prior art or yet-to-be invented – and every doctor who even looks at an ordered test result necessarily infringes. Respondents' own listing of hypothetical instances where the correlation allegedly could be used without infringing in fact shows the claim's prohibitive sweep. Respondents postulate that doctors might administer vitamins to people suspected of having elevated homocysteine, *without* ever testing to confirm that fact. *See* Resp. Br. 41-42. Thus, a doctor can employ the correlation between elevated homocysteine and vitamin deficiencies without infringing only by avoiding inquiry as to whether a patient in fact has elevated homocysteine in the first place. That doctors would have to go to such absurd and dangerous

lengths to avoid Claim 13 shows its impermissible reach.[15] Moreover, most of respondents' hypotheticals depend on prior research establishing that people in a specific population are likely to have elevated homocysteine, but that research itself requires infringing conduct.

The Solicitor General admits that a claim the PTO itself granted is likely invalid because "claim 13 appears to cover all substantial practical applications of the natural phenomenon." U.S. Br. 24. The Solicitor General is correct. But his proposed solution – a remand to determine possible current or future uses of the correlation not encompassed by Claim 13 – is unnecessary, unworkable, and contrary to law. The Court in *Benson* did not require an evidentiary hearing to determine that digital computers were the only substantial practical application of a binary conversion algorithm, *see* 409 U.S. at 71-72, and LabCorp knows of no case endorsing such a rule. Nor would that procedure make sense. Validity rules must be straightforward enough for patent examiners to apply easily and quickly. The PTO cannot seriously advocate that before denying a patent its own examiners must (1) determine all conceivable practical uses of a scientific principle, including divining uses not yet discovered; (2) ascertain the ratio of infringing to non-infringing uses; and (3) decide whether the ratio is sufficiently substantial.[16]

Claim 13 is automatically infringed whenever a doctor looks at a test result and thinks about a scientific principle, and this resulted in an injunction against *all* homocysteine

[15] The Patent itself makes clear that it is dangerous to administer a vitamin – either folate or cobalamin – without first diagnosing which vitamin is deficient in a patient. *See* Pet. Br. 8.

[16] The Solicitor General – but not respondents – suggests that Claim 13 might be valid because it only covers assays of body fluids. U.S. Br. 25. But LabCorp was enjoined from conducting *any* homocysteine tests. In any event, one cannot patent a correlation simply by limiting it to one input; Einstein, for example, could not have patented his equation by limiting it to one kind of matter.

testing by any method. No more is required to determine that the claim has an impermissible preemptive scope.

B. Claim 13 Violates The Disclosure And Enablement Requirements Of The Patent Laws.

Claim 13 also contravenes the disclosure and enablement requirements of Section 112 for largely the same reasons that it fails the subject matter patentability test. *See* Pet. Br. 32-42; *SmithKline*, 403 F.3d at 1361 ("[T]he inevitable failure of the patent to provide public notice * * * stems from the inherently unpatentable nature of the claimed subject matter.") (Gajarsa, J., concurring). Claim 13 is not definite because it does not define any specific "assay," or what "correlating" means beyond recognition of a scientific principle. And it is neither sufficiently enabled nor described because the claim and its specification fail to identify "with clearness and precision," *Tyler* v. *City of Boston*, 74 U.S. (7 Wall.) 327, 330 (1868), any invention – beyond the scientific relationship between elevated homocysteine and vitamin deficiencies.

As LabCorp explained in its opening brief, this Court's landmark ruling in *Morse* provides the rule of decision here. In addition to patenting a concededly valid specific device (the telegraph) for printing characters at a distance, Samuel Morse sought to patent more broadly the use of electromagnetism for that purpose. *See* 56 U.S. at 112. As noted (*supra* at 5-6), the Court invalidated that claim under what is now Section 112. The Court explained that an inventor must "specif[y] the means he uses in a manner so full and exact, that any one skilled in the science * * * can, by using the means he specifies * * * produce precisely the result he describes. And if this cannot be done by the means he describes, the patent is void." *Id.* at 119. Morse's broad claim was held void under that rule because "he claims an exclusive right to use a manner and process which he has not described and indeed had not invented, and therefore could not describe when he obtained his patent." *Id.* at 113.

Allowing Morse to claim a scientific principle, rather than the specific device he invented, would have "shut[ ] the door against inventions of other persons," including devices "less complicated – less liable to get out of order – less expensive in construction, and in * * * operation." *Id.* at 113. Under this claim, "there was no necessity for any specification, further than to say that he had discovered that, by using the motive power of electro-magnetism, he could print intelligible characters at any distance" but "no patent could have issued on such a specification." *Id.* at 119. The claim could "derive no aid from the specification filed. It is outside of it, and the patentee claims beyond it." *Id.* at 119-120.[17]

Morse is indistinguishable from this case in every material respect. Claim 8 of Morse's patent and Claim 13 of this Patent both violate Section 112 because they reach well beyond the scope of the patentees' actual inventions to claim more generally any process or device, whether in existence or yet to be developed, that allows one to use a discovered natural phenomenon. Morse sought to monopolize telecommunications devices he did not disclose or enable, and the patentees here have monopolized assay methods they did not disclose or enable. Even the justifications posited for the patents are eerily similar. Morse stated that because the "essence" of his invention was the use of electromagnetism to print characters at a distance, he did not "propose to limit [him]self to the specific machinery or parts of machinery described" in the specification. 56 U.S. at 112. Here, the patentees stated to the PTO that the scientific correlation was the "heart" of their invention, and that because they were the first to detect vitamin deficiencies through a total homocysteine test, they were "entitled to a claim of equivalent scope,

[17] This was an application of the settled rule under Section 112 – which respondents ignore – that a claim may cover a process "'but never [its] function or result * * * nor the scientific explanation of [its] operation.'" *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 373 (1996) (citation omitted). *See* Pet. Br. 38-39.

not limited to any particular process steps or methods." J.A. 278, 281. Indeed, the precise evil *Morse* sought to prevent has come to pass in this case: LabCorp has been enjoined from using the new Abbott assay method, even though it is far more efficient than the patentees' own invention.[18]

Respondents' brief contains but a single citation to *Morse*, in a footnote. And what they do say is demonstrably wrong. Respondents contend that *Morse* is distinguishable because "[w]hereas Morse claimed all uses of a natural phenomenon, the '658 patent claims just one." Resp. Br. 39-40 n.19. That mischaracterizes both *Morse*'s patent and this one. Claim 8 of Morse's patent purported to claim "just one" application of a natural phenomenon: namely, "'the use of * * * electromagnetism, however developed, *for marking or printing intelligible characters, signs, or letters, at any distances* * * *.'" *Morse*, 56 U.S. at 112 (quoting patent) (emphasis added). And the Federal Circuit in fact held that Claim 13 is *not* limited to a particular use, but applies whenever a doctor looks at a test result. Pet. App. 18a.[19]

[18] The Solicitor General asserts that Claim 13's "breadth" likely renders it invalid for anticipation under 35 U.S.C. § 102. U.S. Br. 28-30 & n.8. He is right that the claim's overbreadth renders it invalid, but as in *Morse*, the invalidity is under Section 112. Claim 13's vice is not simply that it sweeps in prior art assays, but that it covers *all* conceivable assays including those – like the Abbott method – not even invented when the Patent application was filed. Similarly, the claim at issue in *Morse* contravened what is now Section 112 even though the claim did not read on any prior art given that Morse was the first inventor of the telegraph.

[19] Respondents argue (Br. 40 n.19) that the telephone patent in *Dolbear* v. *American Bell Tel. Co.*, 126 U.S. 1 (1888), is "the more apt analogy." The claim at issue there, however, was "not for the use of a current of electricity in its natural state * * * but for putting a continuous current, in a closed circuit, into a certain specified condition, suited to the transmission of vocal and other sounds, and using it in that condition for that purpose." *Id.* at 534. The claim was not "one for the use of electricity distinct from the particular

Respondents otherwise merely parrot the Federal Circuit's reasoning, contending that Claim 13 is sufficiently disclosed and enabled because the specification "explains that '[i]t has been discovered that elevated levels of homocysteine in body tissue correlate with decreased levels of cobalamin and/or folic acid in said body tissue.'" Resp. Br. 16 (quoting S.A. 12). But that is simply a recitation of the natural correlation itself, and under *Morse* such a description will not satisfy Section 112. In *Morse*, it was "impossible to misunderstand the extent of [the] claim," 56 U.S. at 112, but that fact did not save it because neither the claim nor the specification described or enabled an invention beyond the recited natural phenomenon. So too here, nothing in Claim 13 or its specification describes or enables either a specific assay method or specific method of correlating beyond the mere recognition of a natural phenomenon. Claim 13 is therefore overbroad and invalid under Section 112.

Respondents also argue that the specification "describe[s] in detail" how the patentees "established the mutual and reciprocal relationship between total homocysteine and vitamin deficiency," Resp. Br. 15 – that is, how they conducted a clinical study to discover the natural correlation. But that description, however detailed, does not render Claim 13 definite, enabled or sufficiently described. Claim 13 does not inform practitioners how to conduct a clinical study; rather, it merely informs them that the natural correlation exists. Likewise, it is immaterial that the "specification describes in great detail the manner in which to conduct assays." Resp. Br. 17; *see also* U.S. Br. 10 (specification "includes two detailed examples that describe how the applicants measured homocysteine using different assay methods"). One new method of assaying for homocysteine – the patented method in Claims 1 through 12 – is disclosed and enabled. But

process with which it is connected in his patent." *Id.* at 535. In contrast, Claim 13, like Morse's claim, is for a scientific principle divorced from any inventive process or device. *See Benson*, 409 U.S. at 68 (distinguishing *Dolbear* from *Morse* in this way).

Claim 13 claims no particular assay method at all. It claims instead a vague and generic "assay" for homocysteine, sweeping within its scope *every* homocysteine test, whether in the prior art or yet to be invented. As in *Morse*, it is the Patent's utter lack of any further description that renders Claim 13 invalid under Section 112.[20]

III. UPHOLDING CLAIM 13 WOULD STIFLE RATHER THAN PROMOTE INNOVATION.

Respondents barely address, much less dispel, the dangerous consequences of allowing Claim 13 to stand.[21] Instead, they seek to deflect attention from the fatal defects in their own patent by raising the specter that invalidating Claim 13 would call into question "thousands" of other unnamed patents, including in such disparate areas as business methods, genes, and software. Resp. Br. 44 & n.23. Such fear-mongering is unfounded. This case involves a specific patent claim that is invalid under this Court's existing precedents. LabCorp does not ask the Court to overrule *Diehr* or any other case. Indeed, it is telling that the only party asking for the Court to overrule its precedents is one of *respondents'* amici. *See* Franklin Pierce Br. at 21-26.

A ruling invalidating Claim 13 would not directly bear on disparate patents for business methods, genes, or computer software. Each of those patents, like every other patent, would have to be examined on its own merits according to its

[20] Respondents wrongly suggest that the Section 112 inquiry in this case is factual in nature. *See* Resp. Br. 17. Although the determination sometimes entails factual issues, "[t]he ultimate test of patent validity is one of law." *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 280 (1976). As in *Morse*, no disputed factual issues need to be resolved to determine that Claim 13 is overbroad and invalid.

[21] Respondents state that they have abstained so far from suing doctors. But the doctors *are* the infringers under their theory, and this action against LabCorp has had the desired result of monopolizing a critical medical test. Moreover, if Claim 13 is allowed, patentees of other natural correlations would be free to sue doctors.

own claims and specification. The deficiencies of *this* patent claim are clear-cut. Claim 13 involves nothing more than reflexive mental recognition of a natural correlation, preceded by the token activity of ascertaining the input for the correlation. Invalidating that rogue claim would not require invalidation of other types of claims, such as those that fully disclose and enable processes of physical transformation. Nor would such a ruling even affect other kinds of medical diagnostic patents. To the contrary, the very patent at issue in this case claims a diagnostic procedure whose validity has not been challenged: a novel method for diagnosing elevated homocysteine via the specific assay method set forth in Claims 1-12. Thus, as numerous amici have made clear, the Court need not and should not address or opine upon patent claims that are not before the Court in this case.

But if there are in fact other patents that follow the same rudimentary "test plus correlate" formulation of Claim 13, that is even more reason to ensure that the claim does not stand. Such patents on medical or other natural correlations improperly permit parties to monopolize concepts and tests they did not invent and to stifle the free flow of medical and scientific information. *See* Pet. Br. 43-47. The patent laws do not allow that result, and the Court should not sanction it.

CONCLUSION

For the foregoing reasons, and those in the opening brief, the judgment should be reversed.

Respectfully submitted,

JONATHAN S. FRANKLIN*
CATHERINE E. STETSON
JESSICA L. ELLSWORTH
HOGAN & HARTSON L.L.P.
555 Thirteenth Street, N.W.
Washington, D.C. 20004
(202) 637-5766

* Counsel of Record

Counsel for Petitioner

No. 04-607

IN THE
Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS (doing business as LabCorp),

Petitioner,

v.

METABOLITE LABORATORIES, INC. and COMPETITIVE TECHNOLOGIES, INC.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

SUPPLEMENTAL APPENDIX

JONATHAN S. FRANKLIN*
CATHERINE E. STETSON
JESSICA L. ELLSWORTH
HOGAN & HARTSON L.L.P.
555 Thirteenth Street, N.W.
Washington, D.C. 20004
(202) 637-5766

Counsel for Petitioner

GLENN K. BEATON*
GIBSON, DUNN & CRUTCHER LLP
1800 California Street
Denver, Colorado 80202
(303) 298-5773

(Additional Counsel for Respondents on Inside Cover)

Counsel for Respondents

*Counsel of Record

PETITION FOR CERTIORARI FILED NOVEMBER 3, 2004
CERTIORARI GRANTED NOVEMBER 2, 2005

BEST AVAILABLE COPY

United States Patent [19]

Allen et al.

[11] **Patent Number: 4,940,658**

[45] **Date of Patent: Jul. 10, 1990**

[54] **ASSAY FOR SULFHYDRYL AMINO ACIDS AND METHODS FOR DETECTING AND DISTINGUISHING COBALAMIN AND FOLIC ACID DEFICENCY**

[75] Inventors: **Robert H. Allen**, Englewood; **Sally P. Stabler**, Denver, both of Colo.; **John Lindenbaum**, New York, N.Y.

[73] Assignee: **University Patents, Inc.**, Westport, Conn.

[21] Appl. No.: **933,553**

[22] Filed: **Nov. 20, 1986**

[51] **Int. Cl.**[5] **C12Q 1/00; G01N 24/00; A61K 31/68; A61K 31/495**

[52] **U.S. Cl.** **435/4**; 435/18; 436/173; 436/174; 436/8; 436/86; 436/120; 436/825; 514/752; 514/258

[58] **Field of Search** 435/7, 4, 18; 436/505, 436/173, 8, 15, 9, 43, 63, 86, 89, 119, 120, 173, 174, 175, 825; 514/52, 258

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Primary Examiner—Esther M. Kepplinger
Assistant Examiner—Toni R. Scheiner
Attorney, Agent, or Firm—Yahwak & Associates

[57] **ABSTRACT**

Method for determining levels of sulfhydryl amino acids, particularly total homocysteine levels in samples of body tissue from warm-blooded animals, methods of detecting cobalamin and folic acid deficiency using an assay for total homocysteine levels, and methods for distinguishing cobalamin from folic acid deficiency using an assay for total homocysteine levels in conjunction with an assay for methylmalonic acid.

34 Claims, 7 Drawing Sheets

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FIG. 1

methionine synthetase
CH3-S-CH2-CH2-CH(NH2)-COOH
METHIONINE
N,N-dimethyl-glycine
betaine
THF
5,10-methylene THF
HO-B12
MeB12
N5-MTHF
S-ADENOSYL METHIONINE
S-ADENOSYLHOMOCYSTEINE
HS-CH2-CH2-CH(NH2)-COOH
HOMOCYSTEINE
cystathionine γ-synthase
HOOC-CH(NH2)-CH2-S-CH2-CH2-CH(NH2)-COOH
CYSTATHIONINE
HS-CH2-CH(NH2)-COOH
CYSTEINE
SO4-2
CH3-CH2-CO-COOH
α-KETOBUTYRATE
PROPIONYL-CoA
METHYLMALONYL-CoA
METHYLMALONIC ACID
HOB12
deoxyadenosyl-B12
methylmalonyl-CoA mutase
SUCCINYL-CoA
CO2

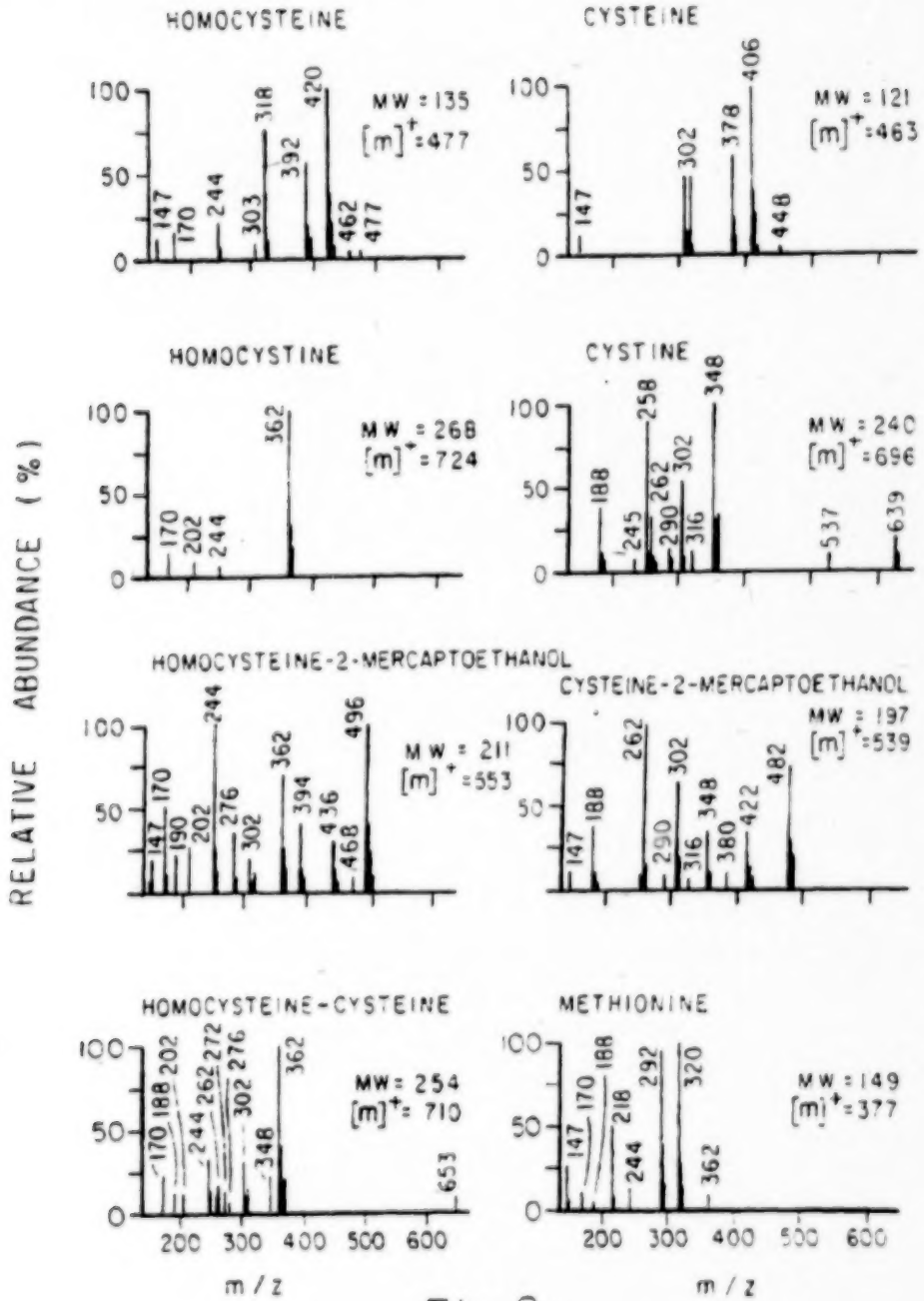

HOMOCYSTEINE
MW = 135
[m]+ = 477
CYSTEINE
MW = 121
[m]+ = 463
HOMOCYSTINE
MW = 268
[m]+ = 724
CYSTINE
MW = 240
[m]+ = 696
HOMOCYSTEINE-2-MERCAPTOETHANOL
MW = 211
[m]+ = 553
CYSTEINE-2-MERCAPTOETHANOL
MW = 197
[m]+ = 539
HOMOCYSTEINE-CYSTEINE
MW = 254
[m]+ = 710
METHIONINE
MW = 149
[m]+ = 377
RELATIVE ABUNDANCE (%)
m/z

Fig. 2

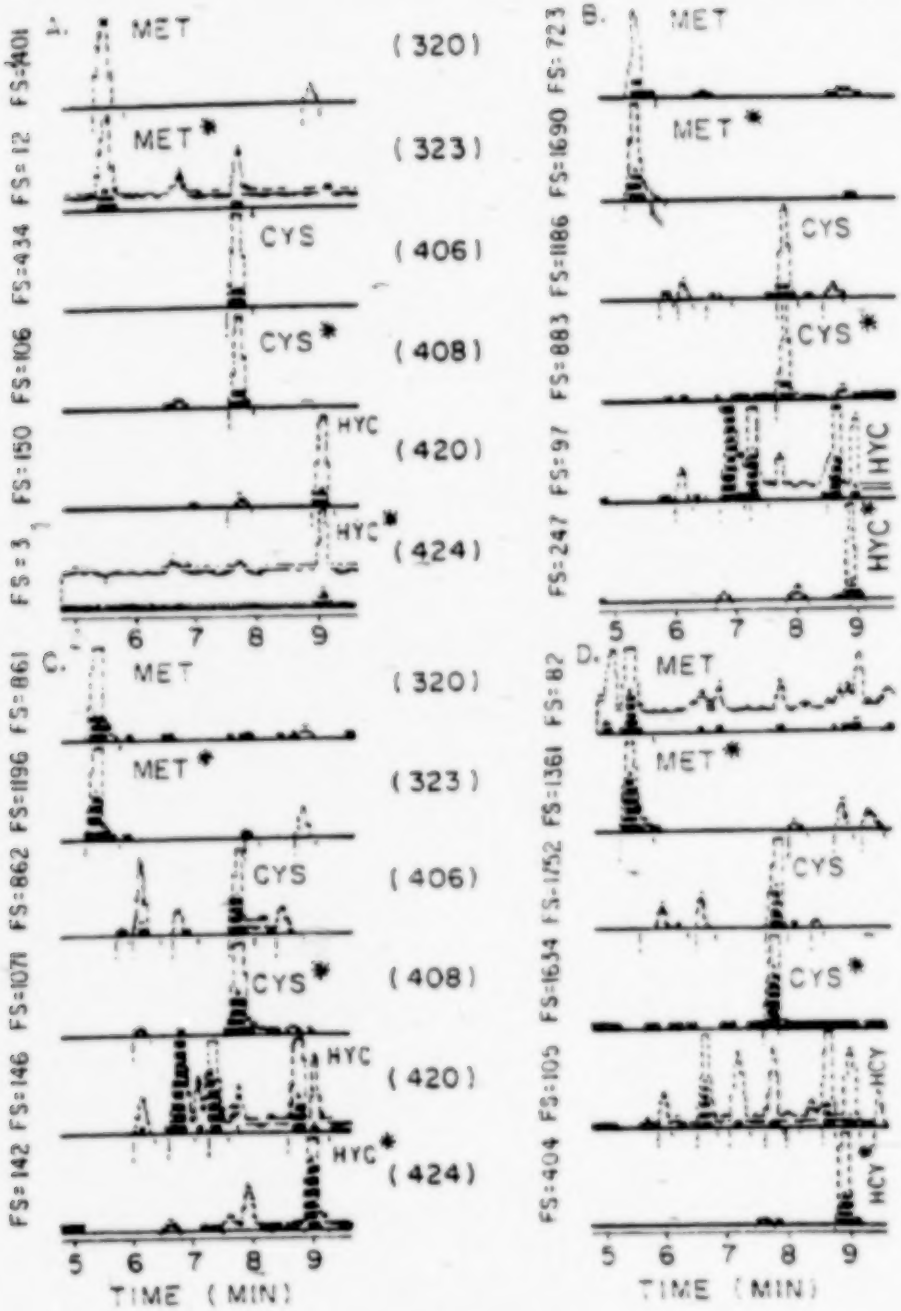

A.
MET
MET*
CYS
CYS*
HYC
HYC*
(320)
(323)
(406)
(408)
(420)
(424)
FS=401 FS=12 FS=434 FS=106 FS=150 FS=3
B.
MET
MET*
CYS
CYS*
HYC
HYC*
FS=723 FS=1690 FS=1186 FS=883 FS=97 FS=247
C.
MET
MET*
CYS
CYS*
HYC
HYC*
(320)
(323)
(406)
(408)
(420)
(424)
FS=861 FS=1196 FS=862 FS=1071 FS=146 FS=142
D.
MET
MET*
CYS
CYS*
HCY
HCY*
FS=82 FS=1361 FS=1752 FS=1634 FS=105 FS=404
5 6 7 8 9
TIME (MIN)

Fig. 3

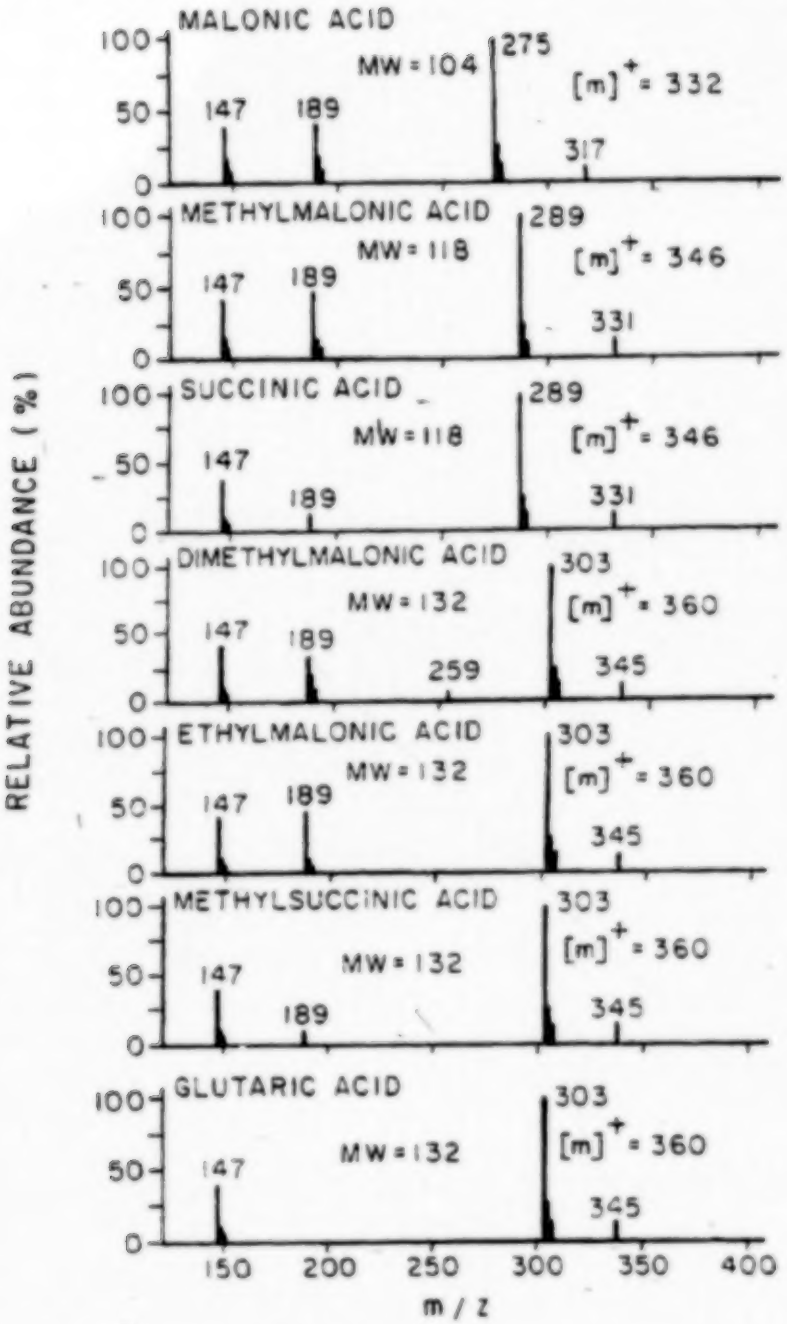

MALONIC ACID
MW = 104
[m]+ = 332
147
189
275
317
METHYLMALONIC ACID
MW = 118
[m]+ = 346
147
189
289
331
SUCCINIC ACID
MW = 118
[m]+ = 346
147
189
289
331
DIMETHYLMALONIC ACID
MW = 132
[m]+ = 360
147
189
259
303
345
ETHYLMALONIC ACID
MW = 132
[m]+ = 360
147
189
303
345
METHYLSUCCINIC ACID
MW = 132
[m]+ = 360
147
189
303
345
GLUTARIC ACID
MW = 132
[m]+ = 360
147
303
345
RELATIVE ABUNDANCE (%)
100
50
0
150
200
250
300
350
400
m / z

Fig. 4

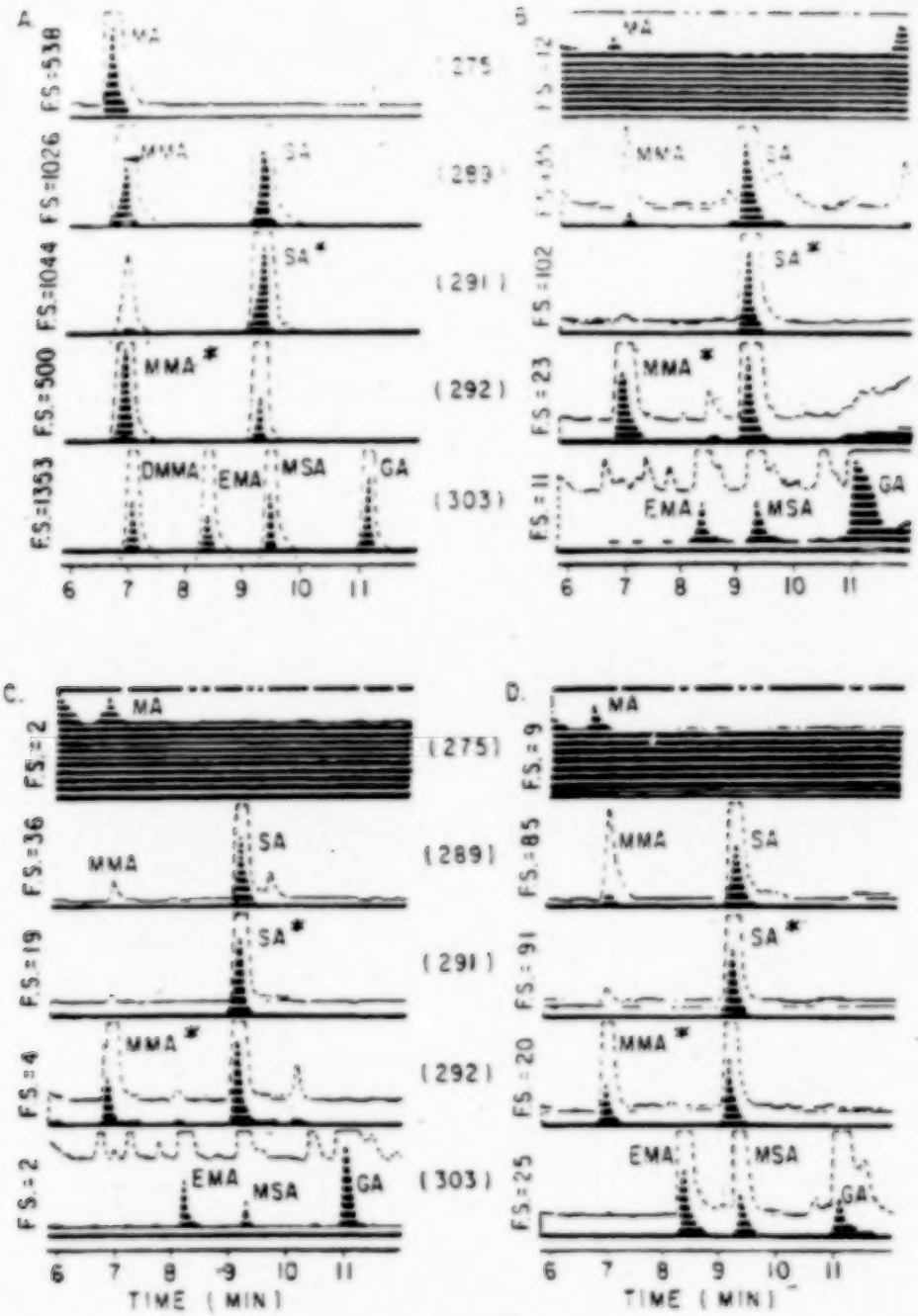

A
B
C
D
MA
MMA
SA
DMMA
EMA
MSA
GA
(275)
(289)
(291)
(292)
(303)
TIME (MIN)
6
7
8
9
10
11

Fig. 5

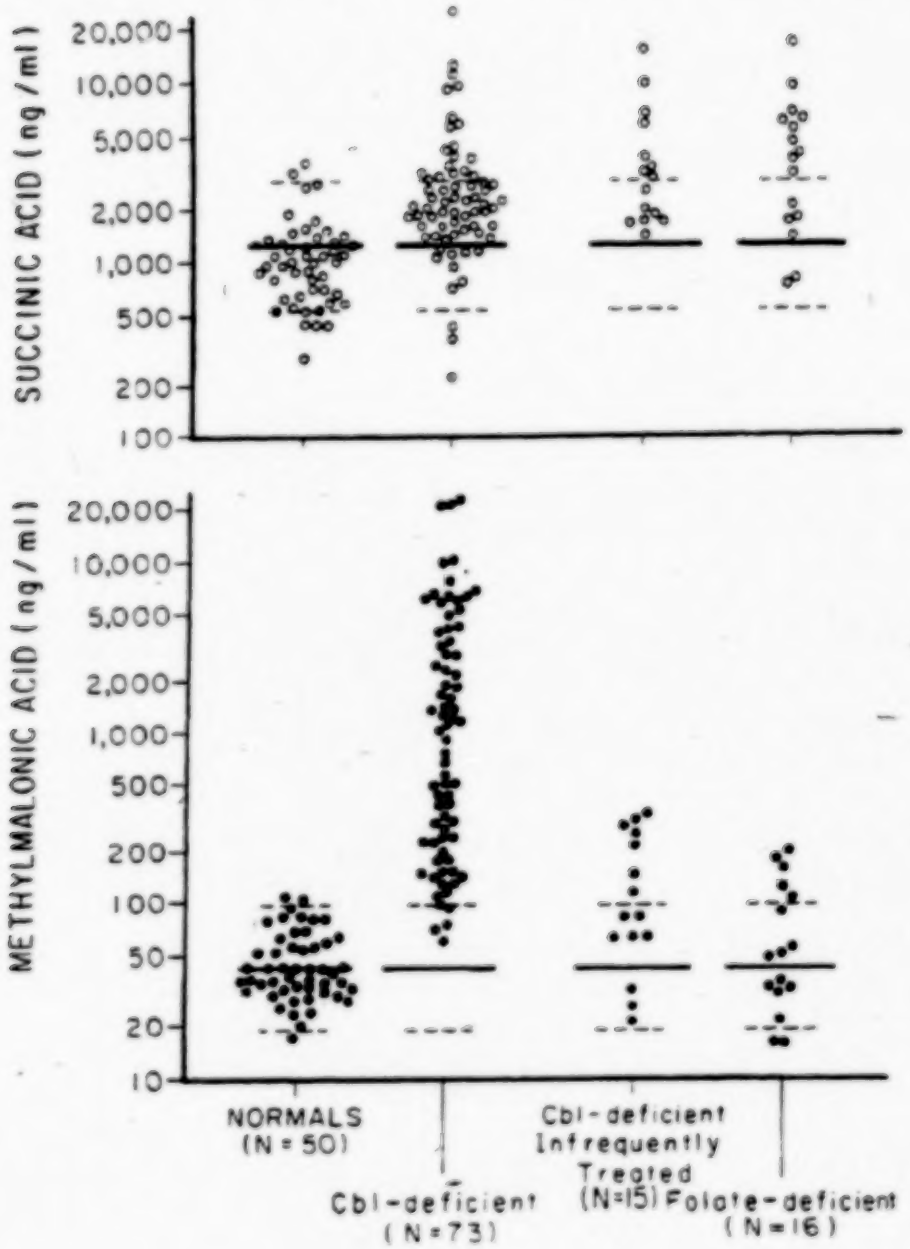

SUCCINIC ACID (ng/ml)
20,000
10,000
5,000
2,000
1,000
500
200
100
METHYLMALONIC ACID (ng/ml)
20,000
10,000
5,000
2,000
1,000
500
200
100
50
20
10
NORMALS (N = 50)
Cbl-deficient (N = 73)
Cbl-deficient Infrequently Treated (N=15)
Folate-deficient (N = 16)

Fig. 6

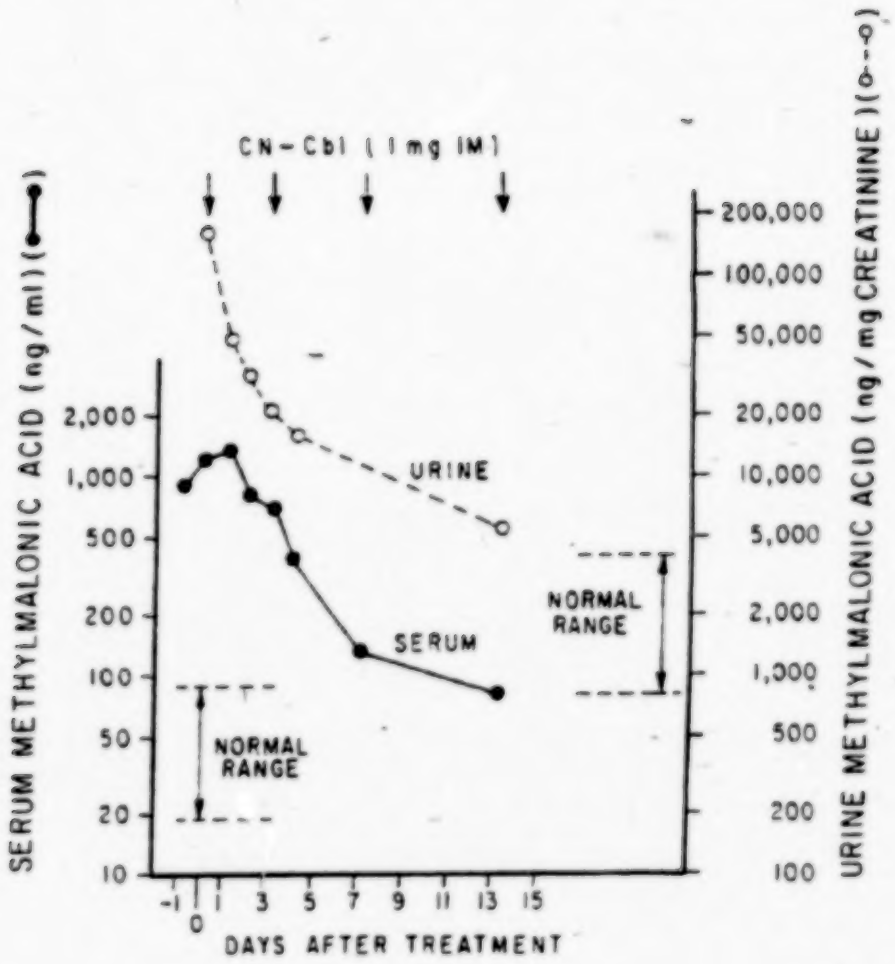

CN-Cbl (1mg IM)
SERUM METHYLMALONIC ACID (ng/ml)
URINE METHYLMALONIC ACID (ng/mg CREATININE)
URINE
SERUM
NORMAL RANGE
NORMAL RANGE
2,000
1,000
500
200
100
50
20
10
200,000
100,000
50,000
20,000
10,000
5,000
2,000
1,000
500
200
100
-1
0
1
3
5
7
9
11
13
15
DAYS AFTER TREATMENT

Fig. 7

ASSAY FOR SULFHYDRYL AMINO ACIDS AND METHODS FOR DETECTING AND DISTINGUISHING COBALAMIN AND FOLIC ACID DEFICENCY

The research leading to this invention was partially funded by grants from the U.S. government.

This invention pertains to methods for quantifying sulfhydryl amino acid concentrations in a sample, for example methods of quantifying total homocysteine concentrations in samples of body tissue from a warm-blooded animal, and methods for determining whether said warm-blooded animal has a cobalamin deficiency, a folic acid deficiency, neither, or both.

BACKGROUND OF THE INVENTION

The sulfhydryl amino acids are metabolized according to a complex set of pathways as shown in FIG. 1.

As can be seen, methylation of homocysteine to form methionine via methionine synthetase requires methylcobalamin (Me-Cbl), also known as methyl-B_{12}. The methyl group is donated by N^5-methyltetrahydrofolate (N^5-MTHF), which is converted to tetrahydrofolate (THF). Conversion of methylmalonyl-CoA to succinyl-CoA via methylmalonyl-CoA mutase requires adenosyl-cobalamin, also known as adenosyl-B_{12} as a cofactor. Thus cobalamin and folic acid are vital cofactors in sulfhydryl metabolism and cobalamin, but not folic acid, is a vital cofactor in methylmalonyl-CoA metabolism.

Accurate and early diagnosis of cobalamin and folate deficiencies in warm-blooded animals is important because these deficiencies can lead to life-threatening hematologic abnormalities which are completely reversible by treatment with cobalamin or folate, respectively. Accurate and early diagnosis of cobalamin deficiency is especially important because it can also lead to incapacitating and life-threatening neuropsychiatric abnormalities; administration of exogenous cobalamin always stops the progression of these abnormalities, almost always leads to significant improvement in symptoms, and frequently leads to their complete correction. The distinction between cobalamin and folate deficiency is often difficult because both deficiencies lead to indistinguishable hematologic abnormalities; the distinction is important because use of the proper vitamin results in the greatest improvement in hematologic abnormalities and, more importantly, only cobalamin will correct the neuropsychiatric abnormalities which are only seen in cobalamin deficiencies. The use of folic acid to treat cobalamin deficiency is extremely dangerous, since some, or all, of the hematologic abnormalities may improve, but neuropsychiatric abnormalities will not improve and may progress, or even be precipitated.

Chapters in leading medical textbooks and articles in leading medical journals teach that cobalamin deficiency should be suspected in individuals with significant anemia (i.e. decreased hematocrit or hemoglobin) in whom the red blood cells are macrocytic (i.e., mean cell volume (MCV)generally > 100 fl), or in individuals who have neurologic abnormalities consisting of peripheral neuropathy and/or ataxia. Many such textbook chapters or journal articles further state that the anemia is typically severe, i.e. hemoglobin ≤8 g %, hematocrit <25%, and size of the red blood cells is greatly increased to levels >110 fl. [See, e.g., Babior, B. M., and H. F. Bunn, in *Harrison's Principles of Internal Medicine* (R. G. Petersdorf, R. F. Adams, E. Braunwald, K. J. Isselbacher, J. B. Martin, and J. D. Wilson, eds.)(McGraw-Hill Book Co., New York, 1983), pp. 1853–1860; Lee, G. R., and H. J. Gardner, in *Textbook of Family Practice*, 3rd Ed. (R. E. Rakel, ed.)(W. B. Saunders & Co., Philadelphia, 1984), pp. 1082–1091.]

Several laboratory tests have been reported as giving abnormal results in patients with cobalamin deficiency or folate deficiency. Such tests include measurements of red blood cell folate [Hoffbrand, A. V., et al., J. Clin. Path. 19:17(1966)]and the "dU suppression test"[Metz, J., et al., Brit. J. Haem. 14:575 (1968)], but neither is widely utilized. It has been known for more than twenty years that methylmalonic acid is excreted in increased amounts in the urine of most patients with cobalamin deficiency and that this abnormality is evidenced by only a few patients with folate deficiency. Because it is believed and taught that cobalamin deficiency should be suspected and can be diagnosed accurately based on the presence and degree of anemia, the presence and degree of macrocytosis, and by the presence and degree of depressed serum cobalamin levels, methylmalonic acid is rarely measured in patients suspected of being cobalamin-deficient. Indeed, it is taught in a leading textbook of medicine and in a leading textbook of hematology that in practice, assay of urinary methylmalonate is rarely necessary. [Beck, W. S., in *Hematology*, 3rd Ed. (W. J. Williams, E. Beutler, A. J. Erslev, and M. A. Lichtman, eds.) (McGraw-Hill Book Co., New York, 1983), pp. 434–465; Beck, W. S., in *Cecil Textbook of Medicine*, *Vol.* 1 (J. B. Wyngaarden and L. H. Smith, Jr., eds)(W. B. Saunders Co., Philadelphia, 1985), pp. 893–900.] While one recent journal article does advocate measurement of urinary methylmalonic acid [Norman, E. J., O. J. Martelo, and M. D. Denton, Blood 59(6):1128–1131 (1982)], analysis of the data in this paper reveals that 26 of the 27 cobalamin-deficient patients were anemic, that 23 of 27 patients had an elevated MCV, and that 12 of 12 patients whose serum cobalamin was measured with the standard improved serum cobalamin assay had values below 100 pg/ml. Thus these patients were all cobalamin-deficient according to standard diagnostic procedures and additional assays would normally have been judged to be unnecessary.

Assays for cobalamin and folate in serum or plasma are the most widely utilized and recommended tests for diagnosing and distinguishing cobalamin and folate deficiency. In the case of cobalamin deficiency, in which the normal range for serum cobalamin is about 200–900 pg/ml, several leading authors state that patients will not only have low serum cobalamin levels, but that these values will be below 100 pg/ml. [See, e.g., Babior, supra; Lee & Gardner, supra; Beck, in *Textbook of Medicine*, supra; and Beck, in *Hematology*, supra].

In 1978, it was discovered that cobalamin analogues are present in human plasma and that their presence could mask cobalamin deficiency because the radioisotope dilution assays for serum cobalamin then in use were not specific for true cobalamin. This problem could be corrected by using pure or purified intrinsic factor as the binding protein in the radioisotope dilution assay for cobalamin and this modification has almost totally replaced assays existing in 1978 that used a non-specific cobalamin-binding protein. See, e.g., U.S. Pat. No. 4,188,189 (Allen), U.S. Pat. No. 4,351,822 (Allen), U.S. Pat. No. 4,451,571 (Allen), and Kolhouse, J. F., H. Kondo, N. C. Allen, E. Podell, and R. H. Allen, N.

Eng. J. Med. 299:785-792 (1978). These improved assays for serum cobalamin are now utilized in thousands of laboratories throughout the world and appear to give low values for all, or almost all, patients with cobalamin deficiency.

The improved assays have been severely criticized, however, because they frequently give low values in patients who lack any evidence of cobalamin deficiency. Because of this, experts in the field have taught that cobalamin deficiency should be considered, and serum cobalamin values should be obtained, only in patients who have hematologic or neurologic abnormalities that are typical of patients with cobalamin deficiency, as discussed above. Schilling and his coworkers, experts in the field of cobalamin deficiency and laboratory diagnosis, have stated:

> "We conclude that the 'improved' vitamin B_{12} assay kits will yield an increased proportion of clinically unexplained low results for serum B_{12}.
>
> It seems prudent for scientific and economic reasons to measure serum vitamin B_{12} only in patients who have hematological or neurological findings that suggest a reasonable probability of vitamin B_{12} deficiency. Measuring serum B_{12} as a screening test in the anemic or the geriatric population will result in a high proportion of low values that cannot be correlated with clinical disease."

Schilling, R. F., V. F. Fairbanks, R. Miller, K. Schmitt, and M. J. Smith, Clin. Chem. 29(3):582-583 (1983)

Thus, the presently available widely used cobalamin assays may frequently provide low serum cobalamin levels in patients who are not truly cobalamin deficient. Such findings are confusing or misleading to the physician and may result in unneccessary and expensive further testing.

Thus, it is generally taught in the art that the clinical spectrum of cobalamin deficiency is relatively narrow and well-defined and that the possibility of cobalamin deficiency should only be considered in those who have concurrent hematological or neurological symptoms, i.e., usually those patients with moderately severe anemia accompanied by moderately severe macrocytosis, and in those patients with peripheral neuropathy and/or ataxia. Routine screening of the general population or those with only moderate anemia, or moderate macrocytosis, or other neuropsychiatric abnormalities, would lead to high numbers of false positives.

It has now been discovered that the clinical spectrum of cobalamin deficiency is much broader than previously recognized and that many cobalamin-deficient patients are not anemic, or only moderately anemic; that in many cases their red blood cells are not macrocytic, or only moderately macrocytic; that in many cases a variety of neurologic abnormalities other than peripheral neuropathy and ataxia are present; and that in many cases the serum cobalamin level is only slightly decreased and may actually be normal, even with the improved assays above using purified intrinsic factor. Accordingly, there is a need for an improved assay for cobalamin deficiency, preferably one in which cobalamin deficiency can be distinguished from folate deficiency.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a representation of the pathways by which sulfhydryl amino acids are metabolized.

FIG. 2 illustrates the mass spectra of sulfhydryl amino acids.

FIGS. 3A, B, C and D illustrate the chromatograms of the t-butyldimethylsilyl derivatives of amino acids.

FIG. 4 illustrates the molecular weights of dicarboxylic acids together with the mass spectra of their t-butyldimethylsilyl derivatives.

FIGS. 5A, B, C and D illustrate the chromatograms of the t-butyldimethylsilyl derivatives of dicarboxylic acids.

FIG. 6 is a graphic representation of serum methylmalonic acid and succinic acid values in cobalamin deficient, folate deficient, and normal subjects.

FIG. 7 is a graphic representation of sequential serum and urine metylmalonic acid levels in a subject with classic pernicious anemia.

SUMMARY OF THE INVENTION

It has now been discovered that an elevated level of total homocysteine in tissues of warmblooded animals correlates both with cobalamin deficiency and with folic acid deficiency; an animal with elevated levels of total homocysteine is likely to have one or both deficiencies but the assay does not distinguish between the two.

In studies of sulfhydryl amino acid metabolism, normal human serum has been shown to contain small amounts of homocysteine-cysteine dimer and protein bound homocysteine. Homocystine has not been detected in normal serum but is present in small amounts in patients with renal insufficiency.

It was previously known that large amounts of homocystine are present in the serum and urine of children with inherited defects in cystathionine synthase who cannot convert homocysteine and serine to cystathionine. These patients also have increased amounts of methionine present in the serum [see, e.g, Mudd, S. H. and H. L. Levy, in *The Metabolic Basis of Inherited Disease*, 5th Ed. (J. B. Stanbury, J. B. Wyngaarden, D. S. Fredrickson, J. L. Goldstein, and M. S. Brown, eds.)(McGraw-Hill Book Co., New York, 1983), pp. 522-559. Large amounts of homocystine also present in the serum and urine of some children with inherited defects involving methionine synthetase, for instance certain children who cannot convert homocysteine and N^5-methyltetrahydrofolate to methionine and tetrahydrofolate, respectively. These patients have low levels of methionine in their serum. In these patients the inherited defects were due to (1) 5,10-methylenetetrahydrofolate reductase deficiency (inability to synthesize N^5-methyltetrahydrofolate, one of the substrates for methionine synthetase); (2) inability to synthesize methyl-cobalamin, a required cofactor for methionine synthetase; and (3) defects in methionine synthetase itself [see, e.g, Mudd, S. H., in *Heritable Disorders of Amino Acid Metabolism: Patterns of Clinical Expression and Genetic Variation*, (W. L. Nyhan, ed.)(John Wiley & Sons, New York, 1974), pp. 429-451]. On the other hand, homocystine has not previously been detected in the urine or serum of other children with inherited defects involving methionine synthetase activity due to an inherited defect in the ability to transport cobalamin to cells (e.g. transcobalamin II deficiency), or to an inherited defect in the intracellular transport of cobalamin where cobalamin is trapped within lysosomes. Large amounts of homocysteine or homocystine have been found in the serum and urine of a few children with life-threatening cobalamin deficiency [see, e.g., Shipman, R. T., R. R. W. Townley, and D. M. Danks, Lancet 1(2):693-694(1969), Frader, J., B. Reibman, and

D. Turkewitz, N. Eng. J. Med. 299:1319(1978); Mudd, S. H., in *Heritable Disorders*, supra; Mudd, S. H., in *Metabolic Basis*, supra; Hollowell, J. G., Jr., W. K. Hall, M. E. Coryell, J. McPherson, Jr., D. A. Hahn, Lancet Dec. 27, 1969, p. 1428; Higgenbottom, M. C., L. Sweetman, and W. L. Nyhan, N. Eng. J. Med. 299(7):317–323 (1978); Davis, J. R., J. Goldenring, and B. H. Lubin, Am. J. Dis. Child. 135:566(1981); Hoey, H., J. C. Linnell, V. G. Oberholzer, and B. M. Laurance, J. Royal Soc. Med.75:656 (1982)]. In other infants with life-threatening cobalamin deficiency, amino acids in urine and/or serum were found to be normal and no homocystine was found [see, e.g., Graesbeck, R., R. Bordin, I. Kantero and B. Kuhlbaeck, Acta Medica Scandinavica 167(4):289 (1960); Lampkin, B. C. and A. M. Mauer, Blood 30(4):495 (1967); Lambert, H. P., T. A. J. Prankerd, and J. M. Smellie, Q. J. Med. 30(117):71(1961); Sievens, C. J., Ugesk. laeger 125:1744 (1963)] nor was it found in the urine of a child with life-threatening folate deficiency [Corbeel, L., G. Van den Berghe, J. Jaeken, J. van Tornout, N. R. Eeckles, Eur. J. Ped. 143: 284–290(1985)]. Homocystune has not previously been reported in the serum or urine of children with moderate or mild cobalamin or folate deficiencies nor has it previously been reported in the serum or urine of adults with life-threatening, moderate, or mild cobalamin or folate deficiencies.

It has also been discovered that the serum folate level is not reduced in many alcoholic patients with folate deficiency and that the measurement of total homocysteine provides an additional and more accurate indication of folate deficiency in many of these patients. It was previously known that homocysteine was elevated in the urine and/or serum of some children with inherited deficiency of folate metabolism [see, e.g. Mudd, S. H., in *Heritable Disorders*, supra; Mudd, S. H. in *Metabolic Basis*, supra], but it was not previously known that homocysteine was elevated in the urine or serum of children or adults with folate deficiency.

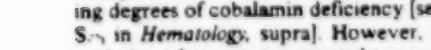
It has additionally been discovered that it is possible to determine whether an animal has cobalamin deficiency, folic acid deficiency, both, or neither, based on a combination assay comparing total tissue homocysteine and methylmalonic acid levels with normal levels. While both folic acid deficiency and cobalamin deficiency result in elevated total homocysteine levels, cobalamin deficiency will also elevate methylmalonic acid levels whereas folic acid deficiency will not. It was previously known that methylmalonic acid is elevated in the serum and/or urine of many children with inherited defects in cobalamin metabolism or cobalamin transport and in urine of children and adults with varying degrees of cobalamin deficiency [see, e.g., Beck, W. S., in *Hematology*, supra]. However, it has not previously been known or suggested to use an assay for methylmalonic acid in combination with an assay for homocysteine to diagnose and/or distinguish cobalamin and folate deficiencies. We have now discovered this combined assay is in fact extremely useful in diagnosing cobalamin deficiency in patients with varying degrees of anemia, macrocytosis, depression of the serum cobalamin level, and varying kinds of neuropsychiatric abnormalities.

It has been discovered that elevated levels of homocysteine in body tissue correlate with decreased levels of cobalamin and/or folic acid in said body tissue. Accordingly, assays for homocysteine can be used to determine the presence or absence of cobalamin and or folic acid deficiency in warm-blooded animals. Suitable assays for this purpose include any assays capable of determining levels of homocysteine in body tissues, preferably body fluids, preferably urine or blood. Serum and plasma are particularly preferred.

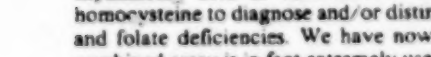
There are several different known assays suitable for use in determining levels of homocysteine in urine or blood, however, none has ever before been used to detect cobalamin or folic acid deficiency. See, e.g. Satre, R. and D. L. Rabenstein, Anal. Biochem. 90:684–692(1978), describing a method of measuring reduced and total cysteine in urine and total cysteine and homocysteine in the nonprotein fraction of plasma, in order to screen for certain congenital disorders of sulfur metabolism such as cystinuria, cystinosis, and homocystinuria and in the monitoring of their treatment. This method comprises subjecting a sample of body fluid to high performance liquid chromatography with an electrochemical detector set to respond to thiol groups, and comparing the results with a standard curve to determine the amount of target compound present in the original sample. In this procedure standards are run separately rather than simultaneously mixed with the target compound; it is thus not possible to insure that the recovery of the target and standard are equivalent. Another suitable procedure, described by Refsum, H., S. Helland, and P. M. Ueland, Clin. Chem. 31(4):624–628 (1985) comprises converting any homocysteine present in the sample to labelled S-adenosylhomocysteine by exposure to radioactively labelled S-adenosine and S-adenosylhomocysteine hydrolase, and quantifying said labelled S-adenosylhomocysteine by appropriate detection means. Suggested uses include monitoring homocysteine metabolism in the management of malignant disease and during treatment with the antifolate drug methotrexate, monitoring of the inherited disease homocystinuria, and monitoring serum homocysteine in plasma of post-menopausal women. The procedure has never been used to monitor homocysteine to detect or measure cobalamin or folic acid deficiency. Again, the procedure uses no internal standard, and thus it is not possible to insure that the recovery of the target and standard are equivalent.

DETAILED DESCRIPTION OF THE INVENTION

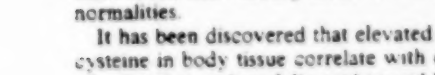
A much more sensitive and accurate procedure for measuring levels of homocysteine in serum or urine is the following novel assay for total sulfhydryl amino acids. Sulfhydryl amino acids are those containing the —SH moiety, e.g. homocysteine (Hcys) of the formula



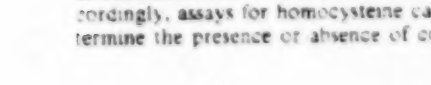
and cysteine (Cys) of the formula



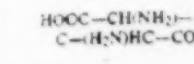
Sulfhydryl compounds are characterized by a natural tendency to combine via disulfide bridges to form dimers, e.g. cystine of the formula



homocystine of the formula



and homocysteine-cysteine of the formula



In the presence of proteins, both homocysteine and cysteine form complexes with free sulfhydryl groups on the protein molecule; in samples derived from tissues, such protein complexes may tie up most of the cysteine and homocysteine present. Assays for total sulfhydryl amino acids are complicated by the ease with which these amino acids form such complexes. Reduction is required for release and subsequent assay of protein bound sulfhydryl compounds but it appears likely that both amino acids might reform new disulfides to a significant extent after their initial reduction. The reformation of disulfide bonds could be quite variable and cannot be assessed or compensated for by the use of a non-sulfhydryl containing amino acid as an internal standard. Any assay for total sulfhydryl amino acids in a sample must take such dimers and complexes into account.

Accordingly, the present invention provides a preferred method of assaying the total cysteine and/or total homocysteine in a given sample using mass spectroscopy. The term "total cysteine" or "total homocysteine" refers to the total amount of cysteine or homocysteine, respectively, present in both free and complexed forms. For convenience, the following discussion will use homocysteine as an example, but the same procedure works for cysteine as well. The given sample containing endogenous homocysteine is combined with a sufficient amount of reducing agent to insure complete randomization of the endogenous homocysteine and the amount of total homocysteine is measured by appropriate means. Preferably, the given sample is first combined with an internal reference standard comprising a known amount of a compound which behaves analagously to the homocysteine but which is labelled with a stable isotope marker. A sufficient amount of reducing agent is added to insure complete randomization of the endogenous homocysteine and reference standard and the amounts of homocysteine and labelled reference standard present are measured with a mass spectrometer. Assuming that the endogenous homocysteine and reference standard occur at the same relative ratio throughout the procedure, this ratio can be calculated from the mass spectrometry readings and applied to the known amount of standard in the original sample to calculate the total amount of endogenous homocysteine originally present. As mentioned above, the same procedure works for cysteine; it is also possible to run an assay for homocysteine and cysteine (or any other amino acid) concurrently as long as each has its own appropriate internal standard.

The internal reference standard is any suitable compound which will behave identically with the endogenous target compound throughout the procedure up to analysis on the mass spectrometer, but which is distinguishable under mass spectrometric analysis and can be separately measured. Examples of suitable internal references are deuterated or tritiated analogs of the target amino acid to be measured, or deuterated or tritiated compounds sufficiently similar to the target amino acid to be effectively identical for the purposes of this assay, or other analogs of the target amino acid containing sufficient amounts of C^{13} or N^{15} or other stable isotope markers. Thus the labelled reference compound is indistinguishable from the unlabelled target during handling but will provide different and distinct ions for quantification on the mass spec. Examples of preferred compounds for this assay are, deuterated forms of cysteine, e.g. D,L-[3,3,3',3'-$^2H_4$]cystine and deuterated homocysteine, e.g. D,L-[3,3,3',3',4,4,4',4'-$^2H_8$]homocysteine. Compounds suitable for use as internal standards are available from, e.g. Merck Sharp & Dohme.

Quantification is based on the assumption that the ratio of measured target compound to measured internal standard is the same as the ratio of the total unknown amount of target compound in the initial sample was to the total amount of added internal standard. This assumes the same recovery rate for both the target and the internal standard. In the case of sulfhydryl compounds, recovery depends at least partially on the various possible forms free and complexed, that the sulfhydryl amino acids can take. Accordingly, for each assay it is crucial that the relative ratio of target and internal standard in the free state and in each possible complexed state be the same; this assures that the same relative percent of target and internal standard will be lost (and recovered). Therefore a reducing agent is added to the initial sample containing both the target and the internal standard; sufficient reducing compound is added to cleave all the disulfide bridges so that all the sulfhydryl amino acids are in their free state. A compound which will prevent rejoining of the disulfide bridges can be added, e.g. iodoacetate, iodoacetamide, or iodopropane, to insure that all sulfhydryl amino acids will remain in the free form. Alternatively, the compounds are allowed to reform disulfide bridges at will, with the assumption that the target and standard sulfhydryl amino acids will form identical types and numbers of such complexes, so that there is the same ratio for the amount of target and internal standard sulfhydryl amino acid in the free state, in each possible complex, and in the amounts of target and internal standard measured by the mass spectrometer, as was in the original sample. Suitable reducing agents are those capable of breaking the disulfide bonds without destroying the remainder of the molecule, e.g., 2-mercaptoethanol, dithiothreitol, and sodium borohydride.

Optionally, it may be necessary or desirable to partially purify the target amino acid and the internal standard either before or after the addition of the reducing agent. Any means known for the purification and separation of amino acids, e.g. filtration, column chromatography, anion and/or cation exchange chromatography, gas chromatography, liquid chromatography, high pressure liquid chromatography, molecular sieving, etc., may be used. Methods of selecting suitable separation and purification techniques, and means of carrying them out, are known in the art. See, e.g., Labadarios, D., I. M. Moodie, and G. S. Shephard, J. Chrom. 310:223-231 (1984) and references cited therein; Shahrokhi, F., and C. W. Gehrke, J. Chrom. 36:31-41(1968).

Optionally, it also may be necessary or desirable to modify the target compound and the internal standard to alter or improve certain characteristics to facilitate purification and/or separation. This practice is well-known in the art as derivatization. For example, it may be desired to convert the target and reference compounds to analogs having improved solubility, different charge, increased volatility, etc., to facilitate purification and/or separation before analysis on the mass spectrometer. See, e.g., Knapp, D. R., *Handbook of Analyti-*

cal Derivatization Reactions (John Wiley & Sons, New York, 1979). A preferred procedure involves converting the target and reference compounds to their silyl derivatives to facilitate separation and identification on a combined gas chromatograph/mass spectrometer apparatus. Means and methods of silating compounds for this purpose are known in the art, see, e.g., Knapp, supra; Bierman, C. J., C. M. Kinoshita, J. A. Marlett, and R. D. Steele, J. Chrom. 357:330-334(1986). A preferred method involves combining the target compound with the internal reference, adding reducing agent to effect randomization, partially purifying the resulting mixture of free and complexed sulfhydryl amino acids, dissolving the product in acetonitrile and adding N-methyl-N-(t-butyldimethylsilyl)trifluoroacetamide to achieve silation. The resulting silated sulfhydryl target and reference compounds are then concentrated to provide the sample injected into the GC/mass spectrometer.

Using this procedure on serum, it is possible to achieve sensitivities of about 1 μmol/liter for total homocysteine and the assay is linear over the range of 1-1000 μmol/liter for total homocysteine. The normal range for homocysteine in human serum is from about 7 to about 22 μmol/liter, and in human urine is from about 1 to about 20 μmol/liter. Homocysteine levels above these ranges are indicative of cobalamin and/or folate deficiency; the higher the level, the stronger the indication.

It has also been discovered that by running a second assay, for methylmalonic acid (MMA) levels, either concurrently with the assay for homocysteine or subsequently thereto, it is possible to distinguish between cobalamin and folic acid deficiency. While both cobalamin and folic acid deficiency will raise homocysteine levels, cobalamin deficiency will usually raise methylmalonic acid levels while folate deficiency usually will not. When homocysteine levels are elevated in individuals without inherited defects, at least one of folate or cobalamin is deficient. When MMA is also elevated, cobalamin is usually deficient. Accordingly, when both homocysteine and MMA are elevated, it is likely that cobalamin is deficient (otherwise MMA would be normal) but it is not clear whether or not folate is also deficient (since any contribution by folate deficiency to the total homocysteine elevation may be masked by the effect of the cobalamin deficiency). Conversely, when homocysteine is high but MMA is normal, the elevated homocysteine is likely to be due to folate deficiency since if it were due to cobalamin deficiency, MMA would usually also be high. It is possible in some cases that MMA levels will be elevated due to cobalamin deficiency even before homocysteine levels begin to rise or that homocysteine will be elevated due to cobalamin deficiency before MMA levels begin to rise. The information supplied by this assay is thus a valuable adjunct to early proper diagnosis of these deficiencies.

In this combined homocysteine/MMA assay, homocysteine levels are suitably assayed by any of the means given above. The procedure of the present invention is preferred. The MMA is suitably assayed by the methods of, e.g., Norman, E. J., O. J. Martelo, and M. D. Denton, Blood 59(6):1128 (1982) or Marcell, P. D., S. P. Stabler, J. H. Podell, and R. H. Allen, Anal. Biochem. 150:58-66 (1985). Preferably, the sample is combined with an internal reference standard comprising a known amount of methylmalonic acid labelled with a stable isotope marker, preferably a deuterated analog of MMA. The amount of labelled and unlabelled MMA present is then measured on a mass spectrophotometer and the amount of MMA in the original sample is calculated from the known amount of labelled MMA originally added. As with homocysteine, the labelled and unlabelled MMA may be subjected to partial purification and/or derivatization before analysis on the mass spectrometer. The preferred derivates are silyl analogs; analogs of N-methyl-N(t-butyldimethylsilyl)trifluoroacetamide are particularly preferred.

It is also possible to measure one or more non-sulfhydryl amino acids, e.g. methionine, concurrently with homocysteine, MMA, or both, provided the appropriate internal standards are included. A suitable internal standard for the non-sulfhydryl amino acids is norleucine or a suitably labelled analog of the non-sulfhydryl amino acid.

Once folate and/or cobalamin deficiency has been determined, the progress of treatment can be monitored by repeating the assays periodically during and after treatment. A drop in the level of homocysteine in the serum and/or urine after oral or parenteral administration of cobalamin and/or folate as the case may be, confirms the diagnosis.

A further understanding of this invention can be had from the following non-limiting examples. As used hereinabove and below unless expressly stated to the contrary, all temperatures and temperature ranges refer to the centigrade system and the terms ambient and room temperature refer to about 20°-25° C. The term percent or (%) refers to weight percent and the terms mole and moles refer to gram moles.

EXAMPLE I

Correlation Between Various Clinical Indices and Cobalamin Deficiency

Over a 24 month period (between September, 1983 and September, 1985) we measured serum cobalamin levels in 7,747 patients in response to requests for this test from physicians at two New York City Hospitals (Columbia-Presbyterian Medical Center and Harlem Hospital Center). Of this group, 301 patients had serum levels below 200 pg/ml the lower limit of normal as stated by the manufacturer of the "improved" radioassay kit using purified intrinsic factor (BioRad Laboratories, Richmond, Calif.). In order to determine how many of the patients with low serum cobalamin levels were truly deficient in the vitamin, we attempted to study every patient thoroughly. As often as was possible, we obtained a full clinical (including neurological) evaluation, blood and bone marrow smears, Schilling tests and serum tests for antibodies to intrinsic factor, and then observed the response of the patient to a course of treatment with cyano-cobalamin.

We were able to reach a firm conclusion as to whether or not cobalamin deficiency was present in 138 of the 301 patients. In 79 of the 138, a clinical or hematologic syndrome, or both, was present that clearly responded to cyano-cobalamin treatment. These patients were considered to be deficient. An analysis of the clinical presentation of these deficient patients showed a number of surprising findings, in that many did not have the classical hallmark findings of megaloblastic anemia due to cobalamin deficiency. The hematocrit was normal (i.e., anemia was not present) in 34 (43%), nearly half of the patients. Moderately severe anemia (Hct <24% or hemoglobin <8 g/dl) was only present in 16

(or one-fifth) of the 79 patients. In 36 patients (45.6%), there were no symptoms present that could be attributed to cobalamin deficiency. The white blood count was normal in 85%; the platelet count was normal in 76%; the serum bilirubin was normal in 74%, and the serum lactate dehydrogenase (LDH) was normal in 40%. Therefore these laboratory findings, which are thought to be typical of patients with megaloblastic anemia, were often or usually missing in the deficient group. Also, the serum cobalamin was >100 pg/ml in 23 (or 29%) of the deficient patients, indicating that the degree of depression of the serum cobalamin also could not be reliably used to predict accurately whether a patient was deficient. Even an elevated MCV, thought to be so characteristic of cobalamin deficiency, was not seen in 15 (19%) of the deficient patients. In those patients with a high MCV, the degree of elevation of the MCV was often slight: 28 (or 35%) of the 79 patients had MCV's in the 100–110 fl range. Thus, only 36 patients (or 46%) had a markedly elevated MCV (>110 fl).

Among the 138 patients about whom we were able to reach a firm conclusion, there were 59 who clearly showed no response in any way to cyano-cobalamin treatment. These patients were considered not deficient. In this not-deficient group, 13 (or 22%) of the 59 had an elevated MCV, and 6 (or 10%) had a serum cobalamin below 100 pg/ml, a further indication that the MCV or the degree of depression of the serum cobalamin could not be used as reliable indicators of whether patients were deficient in cobalamin.

After we discovered that a substantial number of the deficient patients had only slightly low serum cobalamin levels, i.e., in the 100–200 pg/ml range, we undertook a review of all patients with serum cobalamin levels in the 200 to 300 pg/ml range (low normal). In this way, we discovered several patients that were clearly deficient in cobalamin that had serum cobalamin levels >200 pg/ml.

These findings led us to conclude that large numbers of patients with cobalamin deficiency lack the "typical" clinical and hematologic features usually expected to be present in cobalamin deficiency and that there is clearly a need for new tests that would help establish whether deficiency was indeed present.

We then measured serum levels of homocysteine and methylmalonic acid in the specimens from the 79 deficient and the 59 non-deficient patients. Levels of both homocysteine and methylmalonic acid were clearly elevated (homocysteine, above 30 uM and methylmalonic acid, above 150 ng/ml) in 60 (76%) of the 79 deficient patients. The homocysteine level was clearly elevated (without clear elevation of the methylmalonic acid level) in 10 (13%) of the 79, and the methylmalonic acid level was clearly elevated (without clear elevation of the homocysteine level) in 4 (5%) of the patients. In the remaining 5 of the 79 deficient patients (6%), neither test was clearly elevated.

In contrast, in the 59 not deficient patients, both tests were clearly elevated in 1 patient (2%); only the homocysteine was clearly elevated in 6 (10%); and only the methylmalonic acid level was clearly elevated in 9 (15%). In the remaining 43 patients (73%), neither test was clearly elevated. Even in the minority of the non-deficient patients in whom one or both tests was clearly elevated, the tests proved diagnostically useful. Eleven of the 16 patients with clear elevations of one or both tests proved to have underlying disorders of cobalamin absorption, such as pernicious anemia, severe atrophic gastritis and ileal disease, with the potential to cause cobalamin deficiency at some later time. Such patients need to receive prophylactic cyanocobalamin treatment. An additional 2 patients of the 16 had underlying folic acid deficiency to explain the elevation of serum homocysteine.

These tests also appear to be useful in the diagnosis of folate deficiency. In 120 consecutively studied alcoholic patients with anemia, bone marrow examinations were done. In 38 patients the bone marrow smear was megaloblastic. After one patient who had cobalamin deficiency was excluded from the analysis, the remaining 37 patients were considered highly likely to have folic acid deficiency. The serum folate concentration (the most widely used diagnostic test for folate deficiency) was low in only 15 of the 37 patients (41%), whereas the serum homocysteine was clearly elevated in 27 (73%) of the 37 patients. Thus, the serum homocysteine was found to be a more sensitive test for detecting folate deficiency than the serum folate concentration. In 15 patients with megaloblastic bone marrows in whom the red cell folate concentration (RCF) was measured, the RCF was low in 10 of the 15 (67%) and the serum homocysteine was clearly elevated in 13 (87%). Thus, the serum homocysteine assay also was more sensitive than the red cell folate assay.

EXAMPLE II

Representative Preferred Procedure for Measuring Homocysteine in Human Serum

Human blood serum is combined with a suitable internal reference standard, e.g. D,L-[3,3,3',3',4,4,4',4'-$^2H^8$]homocystine, now available from Merck Sharp and Dohme Isotopes (Montreal, Canada) and mixed well.

Excess reducing reagent (e.g. 2-mercaptoethanol, dithiothreitol, or sodium borohydride) is then added to insure that all the homocysteine is reduced to the free form. A chelating agent such as EDTA or EGTA may optionally be added to remove any metal ions which may otherwise bind to the free sulfhydryl group. The reaction mixture is stirred and optionally heated at about 25° to about 150° C. for about 1 min to about 60 min to insure complete randomization of the labelled and unlabelled homocysteine.

Protein is then removed by, e.g., heat denaturation, ion exchange chromatography, gel filtration, or preferably by addition of a compound which precipitates proteins, e.g. sulfosalicylic acid, picric acid, ammonium sulfate, etc. The resulting mixture is stirred and centrifuged to remove protein precipitate. If not already acidic, the supernatant is acidified and added to a cation exchange column, e.g. BioRad AG 50W-X8 (200–400 mesh), hydrogen form (BioRad Laboratories, Richmond, Calif.), to remove any negatively charged salts. The amino acids are then eluted, adjusted to a basic pH, and added to an anion exchange column, e.g. BioRad AG1-X8 (100–200 mesh), acetate form, to remove any positive salts. The amino acids are then eluted, dried, and transferred to small sealable vials, preferably with Teflon-lined septum caps. N-methyl-N-(t-butyldimethylsilyl)trifluoroacetamide in acetonitrile is then added, the vials are sealed and left at about 20° to about 150° C. for about 5 min to about overnight, to complete the silation reaction. Preferably, the vials are left at room temperature overnight, or heated at about 80° C. for about 1 hour. Excess derivatizing agent may then be

removed by addition of water (which hydrolyzes the derivatizing agent) and any volatile solvent. The mixture is centrifuged to clear the emulsion and the non-aqueous layer, which contains most of the derivatized compound, is transferred to a clean vial and evaporated almost to dryness, e.g. under nitrogen, to reduce the volume.

The resulting preparation is then injected onto a gas chromatograph/mass spectrophotometer with an injection port temperature of from about room temperature to about 350° C. and a column head of about 5 to about 45 psi. The capillary column is run at about 20° to about 250° C. for about 1 to about 15 min. Thereafter the temperature is raised to about 75° to about 350° C. at about 1° to about 30° C./min. The exact time and temperature at which the homocysteine elutes is determined by first running a known amount of homocysteine. Thereafter the sample is run and data collected in the scanning mode or preferably in the selected ion monitoring mode.

EXAMPLE III

Representative Specific Procedure for Measuring Homocysteine in Human Serum

L-homocysteine and L-cysteine were purchased from Sigma Chemical Co. (St. Louis, Mo.); L-methionine, other amino acids, and N-methyl-N-[t-butyldimethylsilyl]trifluoroacetamide were obtained from Pierce Chemical Co. (Rockford, Ill.); D,L-[3,3,3',3',-4,4,4'4'-$^2H_8$]homocystine (98.4%) was obtained by a custom synthesis from Merck, Sharp and Dohme Isotopes (Montreal, Can.); and D,L-[3,3,3',3'-$^2H^4$]cystine (98%) and L-[methyl-$^2H_3$]methionine (98%) were purchased from Cambridge Isotope Laboratories (Woburn, Mass.) Blood samples were obtained from normal healthy blood donors at the Belle Bonfils Blood Bank, Denver, Colo., at the time of blood donation. Consecutive blood donors were chosen such that samples were obtained from five males and five females in each of the following age groups: 18–26, 27–35, 36–45, 46–55, and 56–65 (for a total of fifty samples). The samples were obtained between 9 a.m. and 1 p.m., were allowed to clot at room temperature for 1 to 4 hours, centrifuged at 1500×g for 30 min, and the serum was removed and stored at −20° C. Other samples were obtained from laboratory personnel. They were allowed to clot at room temperature for 0 to 24 hours before centrifugation at 4° C., or were added to heparin or EDTA and allowed to stand at room temperature for 0 to 24 hours before the plasma was collected by centrifugation at 4° C. Sprague-Dawley rats, 250–350 g, were obtained from SASCO, Inc (Omaha, Nebr.) and blood was obtained by intracardiac puncture under ether anesthesia. Serum was collected and stored as described above for the human blood donor samples.

A volume of 50 μl of H_2O containing 5 nmol of D,L-[3,3,4',4',4,4,4',4'-$^2H_8$]homocystine, 25 nmol of D,L-[3,3,3',3'-$^2H_4$]cystine, and 15 nmol of L-[methyl-$^2H_3$]methionine was added to 100 μl of serum. After mixing, 2.5 ml of H_2O containing 158 μg of Na_2EDTA and 100 μl of 2-mercaptoethanol were added followed by mixing and boiling at 100° C. for 15 min. After cooling to room temperature, 100 μl of H_2O containing 25 μg of sulfosalicylic acid, and 25 μl of 6N HCl were added followed by mixing and centrifugation at 1000×g for 15 min. The supernatant was then applied to disposable columns containing 200 μl of the cation exchange resin AG 50W-X8 (200–400 mesh), hydrogen form (BioRad Laboratories, Richmond, Calif.), which had been preequilibrated with H_2O. After washing with 6 ml of H_2O, the amino acids were eluted with 2 ml of 8N NH_4OH. The eluates were applied directly to disposable columns containing 200 μl of the anion exchange resin AG1-X8 (100–200 mesh), acetate form (BioRad Laboratories, Richmond, Calif.), which had been washed and equilibrated with H_2O. After washing with 9 ml of H_2O, the amino acids were eluted in 2 ml of 0.1 ml HCl and taken to dryness in a Speed Vac vacuum concentrator (Savant Instruments, Inc., Hicksville, N.Y.). The dried samples were then dissolved in 250 μl of H_2O, transferred to 300 μl Reacti-vials (Pierce Chemical Co., Rockford, Ill.) and taken to dryness in the vacuum concentrator.

The t-butyldimethylsilyl derivatives of the amino acids were prepared by adding 10 μl of acetonitrile and 10 μl of N-methyl-N-(t-butyldimethylsilyl)trifluoroacetamide to each vial, sealing them with Teflon-lined septum caps, and allowing them to stand at room temperature (22° C.) overnight or heating them to 80° C. for 1 hour. Hexane, 100 μl, was added, and after vortexing for 10 sec, H_2O, 20 μl, was added to hydrolyze any unreacted derivatizing agent. After vortexing for an additional 10 sec, the samples were centrifuged at 1000×g for 5 min, and the upper hexane layer was decanted, transferred to microcentrifuge tubes, and dried to approximately 10 μl by applying a stream of nitrogen. Care was taken to avoid complete dryness, since this results in a major loss of the derivatives. Approximately 2 μl was injected onto the capillary column via the falling-needle injector.

Sample analysis was performed on a Hewlett-Packard (Palo Alto, Calif.) 5992B gas chromatograph-mass spectrophotometer equipped with a 9825B calculator, a 9876A printer, and a molecular jet separator. The injection port was modified to accept a falling-needle injector, and an auxiliary make-up carrier gas line was supplied to the jet separator. Sample resolution was achieved on a Durabond DB-1 fused silica capillary column (30 m×0.25 mm i.d., 0.25 um film thickness) from J & W Scientific, Inc. (Rancho Cordova, Calif.)

The gas chromatograph-mass spectrophotometer was operated under standard autotune conditions with an injection port temperature of 250° C. and a column head pressure of 26 psi. The capillary column was equilibrated at 180° C., and 1 min after sample injection was increased to 276° C. at 8° C./min. Data were collected from 4.8 to 9.6 min using the selected ion monitoring mode. The following $[M-57]^+$ ions were monitored using a 50 msec dwell time for each: homocysteine monomer, m/z 420.2;[3,3,4,4-$^2H_4$]homocysteine monomer, m/z 424.2; cysteine monomer, m/z 406.2; [3,3-$^2H_2$]cysteine monomer, m/z 408.2; methionine, m/z 320.2; and [methyl-$^2H_3$]methionine, m/z 323.2. Total homocysteine was quantitated by dividing the integrated area of the m/z 420.2 peak that eluted at approximately 8.9 min (the exact times were determined daily with standards) by the integrated area of the m/z 424.2 peak that eluted at the same time, and then multiplying by 100 umol/liter, which is the equivalent amount of [3,3,4,4-$^2H_4$]homocysteine monomer that was added to each sample. Total cysteine was quantitated in the same manner utilizing the m/z 406.2 and m/z 408.2 peaks that eluted at approximately 7.7 min and multiplying their ratio by 500 umol/liter, which is the equivalent amount of the [3,3-$^2H_2$]cysteine monomer added to the samples

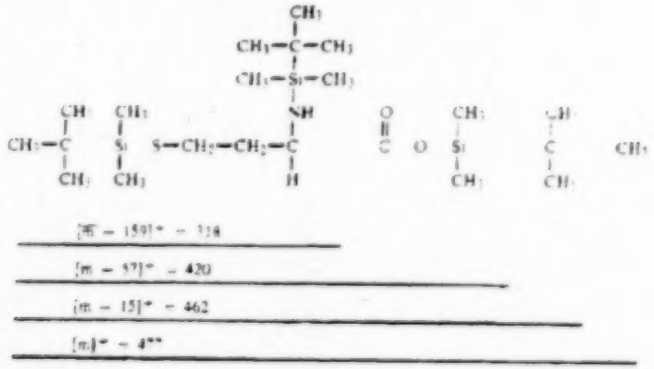
Methionine was quantitated in the same manner utilizing the m/z 320.2 and m/z 323.2 peaks that eluted at approximately 5.4 min and multiplying their ratio by 150 μmol/liter, which is the amount of [methyl-$^2H_3$]methionine added to the samples. The integrated areas for the three internal standard peaks, i.e. the m/z 424.2, m/z 408.2, and m/z 323.2 peaks eluting at about 8.9, 7.7, and 5.4 min, respectively, were corrected for the amounts contributed to them by endogenous total homocysteine, endogenous total cysteine, and endogenous methionine as a result of naturally occurring isotope abundance. These corrections, which were determined with unenriched homocysteine, cysteine, and methionine on a daily basis were as follows: (i)approximately 1.5% of the area of the m/z 420.2 peak at 8.9 min was present as a m/z 424.2 peak at 8.9 min, (ii) approximately 21.4% of the area of the m/z 406.2 leak at 7.7 min was present as a m/z 408.2 peak at 7.7 min, and (iii) approximately 3.1% of the area of the m/z 320.2 peak at 5.4 min was present as a m/z 323.2 peak at 5.4 min.

In experiments in which cysteine-2-mercaptoethanol, homocysteine-2-mercaptoethanol, cystine, homocysteine-cysteine dimer, and homocystine were detected and monitored, the run time was extended to 20 min and the final temperature was increased to 335° C. Spectra for cystine and homocystine were obtained by derivatizing these compounds directly without employing the standard reduction with 2-mercaptoethanol. Spectra for cysteine-2-mercaptoethanol and homocysteine-2-mercaptoethanol were obtained from cystine and homocystine, respectively, in experiments in which these compounds were reduced with-2-mercaptoethanol before derivatization. This latter technique was used to obtain spectra for homocysteine-cysteine dimer except that an equal mixture of homocystine and cystine was reduced by 2-mercaptoethanol followed by derivatization. The sensitivities of the assays were measured by determining, e.g., the ratio of homocysteine monomer to [3,3,4,4-$^2H_4$] homocysteine monomer, at which the standard curves deviate from linearity as described by Zinn, A. B., D. G. Hine, M. J. Mahoney, and K. Tanaka, Pediatr. Res. 16:740–745(1982).

The urinary clearances of total homocysteine, methionine, and total cysteine were determined with the following equation as illustrated for total homocysteine: total homocysteine/creatinine clearance ratio = 100 × [urine total homocysteine (umol/L)/urine creatinine(umol/L)]/[serum total homocysteine (umol/L)/serum creatinine (umol/L)]

The extensive nature of the partial sample purification utilized in this procedure was necessary because of the complex mixture of amino acids and other organic compounds present in serum and urine, and because of the relatively low concentrations of total homocysteine present. Experiments in which known amounts of [methyl-^{14}C]methionine or [U^{14}C]cystine were added to serum and urine samples showed that approximately 70% of the radioactivity from both amino acids was recovered in the final hexane solution at the end of the extensive partial purification and derivatization procedures. Similar recovery studies were not performed for homocystine because radiolabelled homocystine is not commercially available.

The structure and m/z value of the t-butyldimethylsilyl derivative of homocysteine is shown below together with some of the fragmentation positions and the m/z values of the corresponding fragments at $[M]^+$, $[M-15]^+$, $[M-57]^+$, and $[M-159]^+$:



$[M-159]^+ = 318$

$[M-57]^+ = 420$

$[M-15]^+ = 462$

$[M]^+ = 477$

The molecular weights of homocysteine monomer, cysteine monomer, homocystine, cystine, homocysteine-2-mercaptoethanol, cysteine-2-mercaptoethanol, homocysteine-cysteine dimer, and methionine are shown in FIG. 1 together with the mass spectra of their t-butyldimethylsilyl derivatives. The molecular weight of a particular derivative is equal to the molecular weight of the amino acid or disulfide, plus 114 for each t-butyldimethylsilyl group that is bound to each available —COOH, —NH_2, —SH, and —OH group. In the case of homocysteine monomer, cysteine monomer, homocysteine-2-mercaptoethanol, cysteine-2-mercaptoethanol, and methionine, a major peak was present at $[M-57]^+$. In the case of homocystine, cystine, and homocysteine dimer, the major peak was at $[M/2]^+$. A $[M-57]^+$ peak was not observed with homocystine and only small $[M-57]^+$ peaks were observed for cystine and homocysteine-cysteine dimer.

FIG. 3 shows chromatograms of the t-butyldimethylsilyl derivatives of amino acids obtained after reduction from (A) a mixture containing methionine, cysteine, and homocysteine in a ratio of 1:3:1; (B) 100 μl of normal human serum; (C) 100 μl of normal rat serum; and (D) 100 μl of normal human urine. The amino acids studied were: methionine (MET); cysteine monomer (CYS), homocysteine monomer (HCYS); [methyl-$^2H_3$]methionine (MET*); [3,3-$^2H_2$]cysteine monomer (CYS*); and [3,3,4,4-$^2H_4$]homocysteine monomer (HCYS*). MET*, CYS*, and HCYS* were not added to sample A and the peaks bearing their designation represent the amounts contributed to them by MET, CYS, and HCYS, respectively, as a result of naturally occurring isotope abun-

dance. Numbers in parentheses represent the values for m/z that were scanned by selected ion monitoring. The values for "F.S." are relative values for the full scale of the heavy-dashed tracing; the light-dashed tracing is a 10X attenuation. The values determined for endogenous total homocysteine were 18.9, 6.5, and 3.6 μmol/L for B, C, and D, respectively. The values determined for endogenous total cysteine were 369, 173, and 238 μmol/L for B, C, and D, respectively. The values determined for endogenous methionine were 16.8, 60.4, and 3.2 μmol/L for B, C, and D, respectively. FIG. 3A demonstrates that the capillary column gives a complete separation for these three amino acids. The elution profiles of cysteine-2-mercaptoethanol, homocysteine-2-mercaptoethanol, cystine, homocysteine-cysteine, and homocystine are not shown, but they were also present and eluted as single symmetrical peaks with respective elution times of 11.8, 12.9, 16.3, 17.4, and 18.4 min.

Studies with samples of human serum and urine, and rat serum, in which [3,3,3',3',4,4,4',4'-$^2H_8$]homocystine, [3,3,3',3'-$^2H_4$]cystine and [methyl-$^2H_3$]methionine were not added, demonstrated that substances that might interfere with their use as internal standards for quantitation were not present. The sensitivities of the assays were 1 μmol/L for total homocysteine, 5 μmol/L for total cysteine, and 2 μmol/L for methionine under the standard conditions that used 50 μmol/L of [3,3,3',3',4,4,4',4'-$^2H_8$]homocystine, 250 μmol/L of [3,3,3',3'-$^2H_4$]cysune, and 150 μmol/L of [methyl-$^2H_3$]methionine, although the sensitivities could be improved in each case by decreasing the amounts of internal standards added. Assays performed under standard conditions showed that the assays for each of the three amino acids were linear over the ranges of 1 to 1000 μmol/L for total homocysteine, 5 to 5000 μmol/L for total cysteine, and 2 to 2000 μmol/L for methionine.

A chromatogram obtained with 100 μl of normal human serum is shown in FIG. 3B. Endogenous total cysteine is present in the largest amount followed by endogenous methionine and then endogenous total homocysteine. Approximately 70% of the total cysteine was present in the cysteine monomer peak at approximately 7.7 min with the remaining 30% being present (data not shown) as cysteine-2-mercaptoethanol (20%), cystine (9%), and the homocysteine-cysteine dimer (1%) peaks which eluted at later time periods (see above). Approximately 60% of the total homocysteine was present in the homocysteine monomer peak that eluted at approximately 8.9 min with the remainder being present (data not shown) in the homocysteine-2-mercaptoethanol (25%), homocysteine-cysteine dimer (14%), and the homocystine (1%) peaks that eluted later (see above).

The percentages of the various forms of cysteine and homocysteine varied considerably from sample to sample but for a given sample were not altered when the period of boiling with 2-mercaptoethanol was varied from 1 to 60 min or when the amount of 2-mercaptoethanol was varied from 5 to 100 μl. The ratio of endogenous cysteine to [3,3-$^2H_2$]cysteine was essentially identical in all of the various peaks containing cysteine. The ratio of endogenous homocysteine to [3,3,4,4-$^2H_4$]homocysteine was essentially identical in all of the various peaks containing homocysteine. These observations indicate that the endogenous and internal standard forms of cysteine and homocysteine are completely reduced and released from their various disulfide forms, including the forms bound to protein, by the initial 15-min reduction with 100 μl of 2-mercaptoethanol, and that minor but significant amounts of various disulfides are reformed at subsequent stages in the purification and derivatization procedures. This subsequent partial disulfide reformation does not prevent or hinder the quantitation of endogenous total cysteine and endogenous total homocysteine, however, because the internal standards utilized for cysteine and homocysteine, i.e [3,3,3',3'-$^2H_4$]cystine and [3,3,3',3',4,4,4',4'-$^2H_8$]homocystine, are also completely reduced and then participate in the partial disulfide reformation to the same extent as endogenous total cysteine and endogenous total homocysteine. It is possible to quantitate endogenous total cysteine using the ratio of deuterated cysteine to endogenous cysteine in any of the cysteine monomer, cysteine-2-mercaptoethanol, cystine, or homocysteine-cysteine dimer peaks since the values for this ratio are the same in all four peaks for any given sample. It is also possible to quantitate endogenous total homocysteine using the ratio of deuterated homocysteine to endogenous homocysteine in any of the homocysteine monomer, homocysteine-2-mercaptoethanol, homocystine or homocysteine-cysteine dimer peaks since the values for this ratio are the same in all four peaks for any given sample. We have chosen to measure and use the ratios obtained in the cysteine monomer and homocysteine monomer peaks in our standard procedure because they are usually the largest peaks and because they elute earlier than the other peaks.

Preliminary studies indicate that it is possible to couple iodoacetamide to cysteine monomer and homocysteine monomer after the initial reduction step and then proceed with the purification and derivatization procedures in the standard way (data not shown). This modification, which prevents the reformation of disulfides, has not been evaluated in detail, however.

When the reduction with 2-mercaptoethanol is omitted from the standard procedure with human serum, cystine, homocystine, and homocysteine-cysteine dimer peaks are observed that contain endogenous forms of cysteine, homocysteine and both homocysteine and cysteine, respectively. Cysteine-2-mercaptoethanol and homocysteine-2-mercaptoethanol are not detectable under these conditions (data not presented).

Chromatograms obtained with 100 μl of normal rat serum and 100 μl of normal human urine are shown in FIGS. 2C and 2D, respectively, and are similar to the chromatogram obtained with normal human serum (FIG. 2B).

Studies performed with a single sample of pooled normal human serum that was repeatedly frozen and thawed, and assayed on 16 different occasions over a one-month period gave values for the coefficient of variation of 19.7%, 17.4% and 5.6% for the assay of total homocysteine, total cysteine, and methionine, respectively. No significant change or trend in the values for these three amino acids was observed over the one-month period nor have changes been observed when the same serum was assayed on other occasions over a 12 month period.

Values for serum total homocysteine obtained with blood samples that were drawn and immediately centrifuged at 4° C. were the same (10% difference) as those obtained with portions of the same blood samples that were incubated at room temperature for 1 hour prior to centrifugation, but increased by approximately 35% and 75% when the incubation was prolonged for 4

hours and 24 hours, respectively, prior to centrifugation. Values for serum total cysteine were unchanged over the 24 hour incubation period. Values for serum methionine were unchanged at 1 hour and increased by 10% and 25% at 4 h and 24 h, respectively. Plasma collected in EDTA or heparin gave values that were the same as those for serum for all three amino acids at all time periods except in the case of methionine where the values for both types of plasma did not increase at all over the 4 h or 24 h incubation periods. Incubation studies performed with rat serum gave results similar to those obtained with human serum. Values for urine total homocysteine, total cysteine, and total methionine were unchanged when urine samples were incubated at room temperature for 0 h to 24 h.

The values for the actual mean (μmol/L) and range obtained for total homocysteine, total cysteine, and methionine in serum samples from 50 normal human subjects and 50 normal rats, calculated as the mean ±2 S.D. after log transformation to correct for skewness towards higher values were: human serum total homocysteine, 13.0 (7.2–21.7); human serum methionine, 25.5 (13.7–43.5); human serum total cysteine, 261 (174–378); rat serum total homocysteine, 5.6 (3.2–9.6); rat serum methionine, 56 (39–83); and rat serum total cysteine, 190 (131–283). The values for the actual mean (μmol/L or μmol/10 mmol creatinine) and range obtained for urine samples from the same 50 normal human subjects, calculated as defined above, were: human urine total homocysteine, 7.2 (1.4–24.7); human urine total homocysteine /10 mmol urine creatinine, 11.2 (2.0–36.7); human urine methionine, 5.9 (0.4–35.1); human urine methionine/10 mmol creatinine, 6.3 (1.5–19.1); human urine total cysteine, 260 (68–729); human urine total cysteine/10 mmol creatinine,-344 (158–655). The normal ranges for total cysteine and methionine in urine are tighter when expressed as μmol/10 mmol creatinine than when expressed as μmol/L.

Values for total homocysteine and total cysteine were significantly ($P<0.05$) higher in human serum than in rat serum. Values for methionine were significantly ($P<0.05$) higher in rat serum than in human serum.

Human serum total homocysteine, total cysteine, and methionine were not correlated significantly with urine total homocysteine, total cysteine, and methionine, respectively, regardless of whether or not the urine values were expressed as μmol/L or μmol/10 mmol creatinine. Values for serum total homocysteine and serum methionine were, respectively, 20% and 22% higher, in males than in females ($P<0.05$). Values for serum total cysteine, urine total homocysteine, urine total cysteine, and urine methionine were not significantly different for males and females. Values for serum total homocysteine did not correlate significantly with age, hemoglobin, mean corpuscular volume, white blood cell count, platelet count, serum cobalamin, serum folate, serum methionine, serum total cysteine, or serum methylmalonic acid. The highest correlation coefficients were 0.37 between serum total homocysteine and hemoglobin ($P=0.06$) and −0.34 between serum total homocysteine and serum folate ($P=0.06$). The correlation coefficient between serum homocysteine and serum cobalamin was 0.14 ($P=0.44$). The values for serum methionine did not correlate significantly with any of the parameters mentioned above except for hemoglobin where the correlation coefficient was 0.44 ($P<0.05$). The correlation coefficients between serum methionine and serum folate, and serum methionine and serum cobalamin were −0.09 ($P=0.64$) and 0.20 ($P=0.29$), respectively. Serum total cysteine was not significantly correlated with any of the parameters mentioned above except for age and serum methylmalonic acid. The correlation coefficients between serum total cysteine and age, and serum total cysteine and serum methylmalonic acid were 0.38 ($P<0.01$) and 0.30 ($P<0.05$), respectively. Values for urine total homocysteine, urine total cysteine, and urine methionine expressed as μmol/L or μmol/10 mmol creatinine were not significantly correlated with age, hemoglobin, mean corpuscular volume, white blood cell count, platelet count, serum cobalamin, serum folate, serum methylmalonic acid, serum total homocysteine, serum methionine, or serum total cysteine.

We calculated that the mean urinary clearances of total homocysteine, total cysteine, and methionine from human serum relative to the clearance of creatinine were 0.3%, 0.6%, and 0.1%, respectively. These observations demonstrate that only a small fraction of total homocysteine, total cysteine, and methionine present in serum are excreted in the urine, and that levels and relative changes in the concentrations of these amino acids may thus differ between serum and urine in various pathologic conditions.

We have thus developed and demonstrated techniques which make it possible to detect and quantitate total homocysteine and total cysteine in serum from normal humans and rats and in urine from normal humans. Reduction with a suitable sulfhydryl compound such as 2-mercaptoethanol is essential for measuring total homocysteine and total cysteine in serum because 50% to 70% of these amino acids are covalently bound to serum proteins via disulfide linkage. Our studies and those of others indicate that liberation of this bound homocysteine and cysteine occurs rapidly, but our studies also indicate that the formation of new disulfides following reduction occurs to a significant degree. Detection and quantitation based on mass spectrometry is extremely beneficial in this situation, since one can employ stable isotope forms of homocysteine and cysteine themselves as internal standards. These internal standards equilibrate with endogenous total homocysteine and endogenous total cysteine during the reduction step and remain equilibrated during the partial reformation of new disulfides. It is also possible to omit the initial reduction step and thereby detect and measure the concentrations of free homocystine, free cystine, and free homocysteine-cysteine dimer provided the appropriate internal standards are used. It should be possible to utilize our methodology to measure protein bound homocysteine and cysteine separately, although we have not investigated this. It is also possible to measure other amino acids at the same time utilizing additional appropriate internal standards. We have done this in the case of methionine and have found that the methodology is readily applicable to other amino acids.

We have defined normal ranges for total homocysteine in human and rat serum, and human urine. The values for human serum and urine are similar to those reported recently by Refsum, H., S. Helland, and P. M. Ueland, Clin. Chem. 31(4):624–628 (1985). Our values for human serum are approximately 30% higher than theirs, however, and this may be due in part to the use of a stable isotope form of homocysteine as an internal standard in our procedure with the resultant advantages described above, and in part to the fact that total homocysteine values increase somewhat as samples are al-

lowed to clot at room temperature for several hours as in our procedure.

We have also defined normal ranges for total cysteine in human serum and human urine. Our values with respect to human serum are in good agreement with values reported by Malloy, M. H., D. K. Rassin and G. E. Gaull, Anal. Biochem. 113:407–415 (1981), who utilized reduction with dithiothreitol followed by the spectrophotometric determination of endogenous total cysteine. The fact that our values are approximately 20% higher may reflect the inclusion of a stable isotope internal standard in our procedure as discussed above. Our values for human urine total cysteine are similar to those reported by Martensson, J., Metabolism 31:487–492 (1982), who utilized a standard amino acid analyzer.

The normal ranges that we determined for methionine in human and rat serum, and human urine are in excellent agreement with values determined by a number of other investigators who used the amino acid analyzer.

Our values for total homocysteine, total cysteine, and methionine in rat serum are similar to the limited data of other investigators.

The availability of a sensitive and specific method for measuring total homocysteine in human serum will have a number of clinical applications that include the following: (i) determinations of the incidence of elevated values for serum total homocysteine in patients with clinically-confirmed cobalamin or folate deficiency, (ii) determination of total homocysteine levels in the serum of patients with low, borderline, or low normal levels of serum cobalamin or serum folate in order to assess the diagnostic sensitivity and specificity of the serum cobalamin and serum folate assays, (iii) determination of total homocysteine levels in the serum of patients with a variety of neuropsychiatric abnormalities and in the elderly in order to better define the incidence of cobalamin and folate deficiencies in these groups, and (iv) determination of total homocysteine levels in heterozygotes for cystathionine synthetase deficiency in an attempt to develop a better diagnostic test for this heterozygous state which is correlated with an increased incidence of peripheral vascular and cerebrovascular disease. The assay of total homocysteine in human serum is a relatively sensitive measure of both cobalamin deficiency and folate deficiency. The ability to measure total homocysteine in the serum of animals such as the rat will also be useful in studies employing nitrous oxide, cobalamin analogues, folate analogues such as methotrexate, and cobalamin- or folate-deficient diets, all of which interfere with various aspects of cobalamin or folate metabolism and utilization.

EXAMPLE IV

Representative Assay for Methylmalonic Acid

According to the method of Marcell, P. D., S. P. Stabler, E. R. Podell, and R. H. Allen, Anal. Biochem. 150:58–66 (1985)

Methylmalonic, succinic, and glutaric acids were purchased from Sigma Chemical company (St. Louis, Mo.), malonic acid was from J. T. Baker Chemical Co. (Phillipsburg, N.J.), and dimethylmalonic, ethylmalonic, and methylsuccinic acids were from Aldrich Chemical Co. (Milwaukee, Wis.) [Methyl-$^2H_3$]methylmalonic acid (>99%, via custom synthesis) and [1,4-$^{13}C_2$]succinic acid (>99%) were purchased from Merck Sharpe & Dohme Isotopes (Montreal, Canada) [Methyl-^{14}C]methylmalonic acid (via custom synthesis) and [1,4-$^{14}C_2$]succinic acid were purchased from New England Nuclear Corp. (Boston, Mass.). N-Methyl-N(t-butyldimethylsilyl)trifluoroacetamide was obtained from Pierce Chemical Co. (Rockford, Ill.). All solvents were of high-performance liquid chromatography grade from Burdick & Jackson Laboratories, Inc. (Muskegon, Mich.). Blood samples were obtained from normal healthy donors at the Belle Bonfils Blood Bank, Denver, Colo. at the time of blood donation. Consecutive blood donors were chosen such that samples were obtained from five males and five females in each of the following age groups: 18–26, 27–35, 36–45, 46–55, and 56–65, for a total of 20 samples. The samples were obtained between 9 am and 1 pm, were allowed to clot at room temperature for 1 to 4 h and centrifuged at 1500 g for 30 min, and the serum was removed and stored at −20° C. In addition, other samples were allowed to clot for 0 to 24 h before centrifugation. Spot urine samples were collected from the same 50 individuals within 30 min of when the blood samples were obtained and were also stored at −20° C. Sprague-Dawley rats, 250–350 g, were obtained from SASCO, Inc. (Omaha, Neb.) and blood was obtained by intracardiac puncture under ether anesthesia. Serum was collected and stored as described above for the human blood samples.

A volume of 50 μl of H_2O containing 200 ng of [methyl-$^2H_3$]methylmalonic acid and 2000 ng of [1,4-$^{13}C_2$]succinic acid was added to 500 μl of serum or 100 μl of urine, and an additional 400 μl of H_2O was added to the urine samples. The pH was then raised to about 12 by adding 50 μl of 2 N NaOH and 5 ml of diethyl ether was then added, followed by vigorous mixing and centrifugation at 1000 g for 3 min, and the upper ether layer was decanted and discarded. The pH was then adjusted to about 1 by adding 50 μl of 6 N HCl and the samples were extracted twice with 5 ml of diethyl ether as described above. The ether extracts were pooled, taken to dryness by applying a stream of nitrogen in a 40° C. water bath, and then dissolved in 500 μl of H_2O. The entire sample was injected onto a Waters Associates (Milford, Mass.) high-performance liquid chromatography anion-exchange system consisting of a 720 system controller, a 730 data module, two 6000A pumps, a U6K injector, and a Z-module equipped with a Radial Pak SAX cartridge (10 um, 8 mm × 10 cm), and a precolumn (4 × 23 mm) packed with pellicular anion exchanger obtained from Whatman, Inc. (Clifton, N.J.). The mobile phase consisted of 0.05M KH_2PO_4-H_3PO_4, pH 2.0, and 2-ml fractions were collected at a flow rate of 2 ml/min. Fractions 3–5 contained greater than 95% of the methylmalonic acid and succinic acid that was injected based on separate experiments performed with [methyl-^{14}C]methylmalonic and [1,4-$^{14}C_2$]succinic acids, which were used to check the chromatography system on a daily basis. These fractions were pooled, 50 μl of 6N HCl was added to adjust the pH to approximately 1, and the samples were extracted twice with 5 ml of diethyl ether as described above. These ether extracts were pooled, taken to dryness by applying a stream of nitrogen in a 40° C. water bath, dissolved in 150 μl of methanol, and transferred to 300-μl Reactivials (Pierce Chemical Co., Rockford, Ill.), together with a 150 μl methanol rinse. The samples were then taken to dryness in a Speed Vac vacuum concentrator (Savant Instruments, Inc., Hicksville, N.Y.).

The t-butyldimethylsilyl esters of the dicarboxylic acids were prepared by adding 100 μl of acetonitrile and 10 μl of N-methyl-N-(t-butyldimethylsilyl)trifluoroacetamide to each vial, sealing them with Teflon-lined septum caps, and allowing them to stand at room temperature (22° C.) overnight. H_2O, 100 μl, was added to hydrolyze any unreacted derivatizing reagent, followed by the addition of 250 μl hexane, vigorous mixing, and centrifugation at 1000 g for 5 min. The upper hexane layer was decanted, transferred to a separate Reacti-vial, and dried to approximately 5 μl by applying a stream of nitrogen. Care was taken to avoid complete dryness, since this results in a major loss of the derivatives. Approximately 2 μl was injected onto the capillary column of a Hewlett-Packard (Palo Alto, Calif.) 5992B gas chromatograph-mass spectrometer via the falling-needle injector. The gas chromatograph/mass spectrometer was equipped with a 9825B calculator, a 9876A printer, and a molecular jet separator. The injection port was modified to accept the falling-needle injector and an auxiliary make-up carrier gas line was supplied to the jet separator. Sample resolution was achieved on a Durabond DB-5 fused silica capillary column (30 m×0.25 mm i.d., 0.25 um film thickness) from J & W Scientific, Inc. (Rancho Cordova, Calif.). The gas chromatograph/mass spectrophotometer was operated under standard autotune conditions with an injection port temperature of 250° C. and a column head pressure of 22 psi. The capillary column was equilibrated at 160° C. and 6.5 min after sample injection was increased to 188° C. at 8° C./min. Data were collected from 5.8 to 12.5 min using the selected ion monitoring mode. The following $[M-57]^+$ ions were monitored using a 50-ms dwell time for each: malonic acid, m/z 275.2; methylmalonic acid, m/z 289.2; [methyl-$^2H_3$]-methylmalonic acid, m/z 292.2; succinic acid, m/z 289.2; [1,4-$^{13}C_2$]succinic acid, m/z 291.2; dimethylmalonic acid, m/z 303.2; ethylmalonic acid, m/z 303.2; methylsuccinic acid, m/z 303.2; and glutaric acid, m/z 303.2. Methylmalonic acid was quantitated by dividing the integrated area of the m/z 289.2 peak that eluted at approximately 6.6 min (the exact times were determined daily with standards) by the integrated area of the m/z 292.2 peak that eluted at the same time, and then multiplying by 200 ng, which was the amount of the [methyl-$^2H_3$]methylmalonic acid added to each sample. Succinic acid was quantitated in the same manner utilizing the m/z 289.2 and m/z 291.2 peaks that eluted at approximately 9.3 min and multiplying their ratio by 2000 ng, which was the amount of the [1,4-$^{13}C_2$]succinic acid added to the samples. The integrated areas for the two internal standard peaks, i.e. the m/z 292.2 and m/z 291.2 peaks eluting at about 6.8 and 9.3 min, respectively, were corrected for the amounts contributed to them by endogenous methylmalonic acid and succinic acid as a result of naturally occurring isotope abundance. These corrections, which were determined for unenriched methylmalonic and succinic acids on a daily basis, were as follows: (i) approximately 1.9% of the area of the m/z 289.2 peak at 6.8 min was present as a m/z 292.2 peak at 6.8 min, and (ii) approximately 10.8% of the area of the m/z 289.2 peak at 9.3 min was present as a m/z 291.2 peak at 9.3 min.

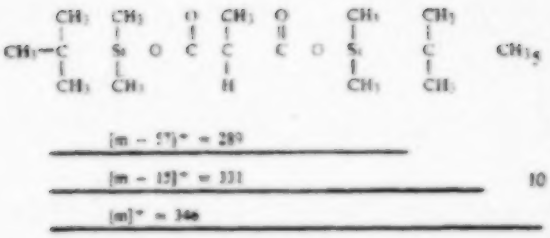
The sensitivity of the assay was measured by determining, e.g., the ratio of methylmalonic acid to [methyl-$^2H_3$]methylmalonic acid, at which the standard curve deviates from linearity as described by Zinn, A. B., D. G. Hine, M. J. Mahoney, and K. Tanaka, Pediatr. Res. 16:740–745 (1982).

The urinary clearance of methylmalonic acid and succinic acid from serum, relative to that of creatinine, was determined with the following equation as illustrated for methylmalonic acid: methylmalonic acid/creatinine clearance ratio = 100 × [urine methylmalonic acid (ng/ml)/urine creatinine (ng/ml)]/[serum methylmalonic acid (ng/ml)/serum creatinine (ng/ml)].

The extensive nature of the partial sample purification utilized in this procedure was necessary because of the complex mixture of organic compounds found in serum, and because of the relatively low concentrations of methylmalonic acid that are present. Procedures using extractions with various organic solvents followed by a further purification with small anion-exchange or reverse-phase columns were unsatisfactory. High-performance liquid chromatography using an anion-exchange resin proved to be very beneficial, since the low pK_a values of the dicarboxylic acids under study resulted in their being retarded at pH 2, while most other compounds were not retarded. Analysis of urine samples may not require the same degree of partial purification as is necessary for serum. Experiments in which known amounts of [methyl-^{14}C]methylmalonic acid and [1,4-^{14}C]succinic acids were added to serum and urine samples showed that 10 to 20% of both dicarboxylic acids were recovered in the final hexane solution at the end of the extensive partial purification and derivatization procedures.

Initial attempts to produce the t-butyldimethylsilyl derivatives of dicarboxylic acids using a mixture of t-butyldimethylchlorosilane/N,N-dimethylformamide/imidazole (Applied Science Laboratories, Inc., State College, Pa.) as described by de Jong, A. P. J. M., J. Elema, and B. J. T. van de Berg, Biomed. Mass Spectrom. 7:359–364 (1980) were unsatisfactory for quantitative work due to marked variations in the degree of derivatization and due to the relative instability of the derivatives. Questions concerning the unexpected ease with which some t-butyldimethylsilyl derivatives, such as esters of certain organic acids, are hydrolyzed have been raised in the past. We found that the pH of the reaction mixture as described by de Jong *et al.* was approximately 1, and that this resulted in the hydrolysis of the newly-formed t-butyldimethylsilyl derivatives of the dicarboxylic acids due to an inability of the imidazole to completely scavenge the HCl produced by the reaction involving the chlorosilane. This problem was only partially corrected by the addition of other acid scavengers such as pyridine. We found, however, that the t-butyldimethylsilyl derivatives prepared with N-methyl-N-(t-butyldimethylsilyl)trifluoroacetamide were obtained in high yield, in a reproducible manner, and were stable for more than a week after their extraction into hexane as described above. This procedure was therefore adopted as our standard method.

The structure and m/z value of the t-butyldimethylsilyl derivative of methylmalonic acid is shown below together with the fragmentation pattern and the m/z values of the major fragments of interest which are at $[M-57]^+$ and $[M-15]^+$.



The molecular weights of malonic, methylmalonic, succinic, dimethylmalonic, ethylmalonic, methylsuccinic, and glutaric acids are shown in FIG. 4 together with the mass spectra of their t-butyldimethylsilyl derivatives. The molecular weight of a particular derivative is equal to the molecular weight of the dicarboxylic acid plus 228 due to the addition of two t-butyldimethylsilyl groups. Peaks representing the entire derivative, i.e., $[M]^+$, were not observed for any of the dicarboxylic acids. Rather, the major peak in each case was $[M-57]^+$, which represented 35–45% of the sum of all the peaks in the m/z range of 100 to 400. Smaller peaks representing $[M-15]^+$ were also observed for each dicarboxylic acid derivative, although the amounts were only 3–6% of the amounts present for the $[M-57]^+$ peaks. Peaks with a value of m/z 147 were observed with all of the dicarboxylic acid derivatives and peaks with a value of m/z 189 were observed with all except for the glutaric acid derivative. Both of these peaks appear to result from fragmentation and rearrangement of portions of the t-butyldimethylsilyl groups themselves, and do not involve portions of the dicarboxylic acids themselves because abundant m/z 147 and m/z 189 peaks were also observed with [methyl-$^2H_3$]methylmalonic acid and [1,4-$^{13}C_2$]succinic acid.

FIG. 5 shows chromatograms of the t-butyldimethylsilyl derivatives of dicarboxylic acids obtained from (A) a mixture containing 1 μg of each acid; (B) 500 μl of pooled normal human serum; (C) 500 μl of normal rat serum; and (D) 100 μl of normal human urine. The acids studied were malonic acid (MA), methylmalonic acid (MMA), succinic acid (SA), [1,4-$^{13}C_2$]succinic acid (SA*), [methyl-$^2H_3$]methylmalonic acid (MMA*), dimethylmalonic acid (DMMA), ethylmalonic acid (EMA), methylsuccinic acid (MSA), and glutaric acid (GA). Numbers in parentheses are the values for m/z that were scanned by selected ion monitoring. Values for "F.S." are the relative values for the full scale of the heavy-dashed tracing; the light-dashed tracing is a 10X attenuation. Values determined for MMA were 56, 92, and 3400 ng/ml for B, C, and D, respectively. Values determined for SA were 1110, 9200, and 19,000 ng/ml for B, C, and D, respectively.

FIG. 5A demonstrates that the capillary column gives a complete separation for all of the derivatives that have the same molecular weight, i.e., methylmalonic acid and succinic acid are completely separated from each other, and dimethylmalonic acid, ethylmalonic acid, methylsuccinic acid, and glutaric acid are completely separated from one another. Methylmalonic acid is not completely separated from dimethylmalonic acid nor is succinic acid completely separated from methylsuccinic acid, but this is not a problem, since, as shown in FIG. 4, these unresolved dicarboxylic acid derivatives have different molecular weights and mass spectra and thus there is no interference when selected ion monitoring is used.

Studies with samples of human serum and urine and rat serum, in which [methyl-$^2H_3$]methylmalonic and [1,4-$^{13}C_2$]succinic acids were not added demonstrated that substances that might interfere with their use as internal standards for quantitation were not present. The sensitivity of the assays were 5 ng for methylmalonic acid and 150 ng for succinic acid under the standard conditions that used 200 ng of [methyl-$^2H_3$]methylmalonic acid and 2000 ng of [1,4-$^{13}C_2$]succinic acid, although the sensitivities could be improved in each case by decreasing the amounts of the internal standards added. Assays performed under standard conditions showed that the assay for methylmalonic acid was linear from 5 to 5000 ng, and that the assay for succinic acid was linear from 150 to 150,000 ng in aqueous samples and in serum samples to which known amounts of the respective acids were added.

A chromatogram obtained with 500 μl of pooled normal human serum is shown in FIG. 5B. Succinic acid is present in the largest amount and malonic, methylmalonic, ethyl malonic, methylsuccinic, and glutaric acids are present in smaller, but readily detected, amounts. Dimethylmalonic acid could not be detected with certainty. Chromatograms obtained with 500 μl of normal rat serum and 100 μl of normal human urine are shown in FIGS. 5C and D, respectively, and are similar to the chromatogram obtained with pooled normal human serum (FIG. 5B).

Studies performed with a single sample of pooled normal human serum that was repeatedly frozen and thawed and assayed on seventeen different occasions over a 10-month period gave values for the coefficient of variation of 26 and 19% for the assay of methylmalonic acid and succinic acid, respectively. No significant change or trend in the values for these two dicarboxylic acids was observed over the 10-month period. Values for serum methylmalonic acid obtained with blood samples that were drawn and immediately centrifuged at 4° C. were the same as those obtained with portions of the same blood samples that were incubated at room temperature for 1 or 24 h prior to centrifugation. Values for serum succinic acid increased over this time period, however, with an approximate increase of 10% being noted after the 1 h room temperature incubation and an approximate 90% increase being noted after the 24 hour incubation. Studies performed with rat serum gave similar results. Values for urine methylmalonic and succinic acids were unchanged when urine samples were incubated at room temperature for 0 to 24 h.

The values for the actual mean (ng/ml) and range obtained for methylmalonic and succinic acids in serum samples from 50 normal human subjects and 95 normal rats, calculated as the mean ±2 S.D. after log transformation to correct for skewness towards higher values were: human serum methylmalonic acid, 41 (19–76); human serum succinic acid, 1270 (580–2420); rat serum methylmalonic acid, 128 (42–295); and rat serum succinic acid 11900 (5420–22800). The values for the actual mean (ng/ml or ng/mg creatinine) and range obtained for urine samples from the same 50 normal human subjects, calculated as defined above, were: human urine methylmalonic acid, 1840 (270–7190); human urine methylmalonic acid/mg urine creatinine, 2010 (810–3630); human urine succinic acid, 25400 (4620–85600); and human urine succinic acid/mg urine creatinine, 2820 (5360–75100). The normal ranges for methylmalonic

and succinic acids in urine are higher when expressed as ng/mg creatinine than when expressed as ng/ml.

Values for methylmalonic and succinic acids were both significantly higher in rat serum than in human serum. Neither human serum methylmalonic acid nor human serum methylmalonic acid per milligram serum creatinine correlated significantly with urine methylmalonic acid or urine methylmalonic acid per milligram urine creatinine. The values for serum and urine methylmalonic acid were not significantly different for males and females and did not correlate significantly with age, hemoglobin, mean corpuscular volume, white blood count, platelet count, serum cobalamin, serum folate, serum creatinine, serum succinic acid, or urine succinic acid. The highest correlation coefficient was −0.25 between serum methylmalonic acid and serum cobalamin (P=0.08). Serum and urine succinic acid levels were not significantly correlated with any of the parameters mentioned above for methylmalonic acid.

We calculated that the mean urinary clearance of methylmalonic acid from human serum relative to the clearance of creatinine was 28%, and the mean urinary clearance of succinic acid from human serum relative to the clearance of creatinine was 13%. This observation supports the concept that most of the methylmalonic acid in serum is metabolized via unknown pathways, as has been observed in experiments in which [methyl-^{14}C]methylmalonic acid was administered to rats via intracardiac injections.

Our studies support the suggestions of de Jong et al. since we have shown that the t-butyldimethylsilyl derivatives of a number of dicarboxylic acids have excellent gas chromatographic and mass spectrometric properties. Initially, we encountered problems of a serious nature due to variable degrees of derivatization and hydrolytic instability, but these problems were solved by substituting N-methyl-N-(t-butyldimethylsilyl) trifluoroacetamide as the derivatizing reagent in place of the t-butyldimethylchlorosilane/N,N-dimethylformamide/imidazole mixture utilized by de Jong et al. This improvement is also applicable to preparing and quantitating t-butyldimethylsilyl derivatives of other compounds of biologic interest that contain carboxylic or other groups that are particularly susceptible to hydrolysis, and to the derivatization and quantitation of other amino acids.

We have developed techniques which make it possible to detect and to quantitate methylmalonic acid in serum from normal humans and rats. We have also defined the normal range for methylmalonic acid in human urine and our values are in general agreement with values obtained with other gas chromatography-mass spectrometry techniques. Our method is also suitable to quantitate malonic, dimethylmalonic, ethylmalonic, methylsuccinic, glutaric, and other dicarboxylic acids in serum and urine, although an appropriate stable isotope internal standard for each dicarboxylic acid should be utilized to ensure optimal quantitative accuracy.

The availability of a sensitive and specific method for measuring methylmalonic acid in human serum has a number of clinical applications that include the following: (i) determination of the incidence of elevated values for serum methylmalonic acid in patients with clinically confirmed cobalamin deficiency, (ii) determination of methylmalonic acid levels in the serum of patients with low, borderline, and low normal levels of serum cobalamin in order to assess the diagnostic sensitivity and specificity of the serum cobalamin assay, and (iii) determination of methylmalonic acid levels in the serum of patients with a variety of neuropsychiatric abnormalities, and in the elderly in order to better define the incidence of cobalamin deficiency in these groups. The assay of methylmalonic acid in human serum is a relatively sensitive measure of cobalamin deficiency, and the ability to measure methylmalonic acid in the serum of animals such as the rat will also be useful in studies employing nitrous oxide, cobalamin analogs, or cobalamin-deficient diets, all of which interfere with various aspects of cobalamin metabolism and utilization.

EXAMPLE V

Assay of Methylmalonic Acid in the Serum of Patients with Cobalamin Deficiency

Serum samples from 50 normal blood donors, 25 males and 25 females, ranging in age from 18 to 65 years were obtained as described in Example II. Patient samples were selected from an extensive serum collection that has been assembled over the past 15 years. The diagnosis of cobalamin (Cbl) deficiency was based on low serum Cbl levels, megaloblastic bone marrow morphology, appropriate hematologic or neurologic abnormalities, and a significant response to treatment with parenteral Cbl. The diagnosis of pernicious anemia was based on an abnormal Schilling test [see, e.g., Beck, W. S., in *Hematology* (W. J. Williams, E. Beutler, A. J. Erslev, and M. A. Lichtman, eds.)(McGraw-Hill Book Co., New York, 1983), pp. 444–445]that corrected with exogenous intrinsic factor and/or the presence of anti-intrinsic factorblocking antibodies in the serum. The diagnosis of folate deficiency was based on low serum folate values, normal or elevated serum Cbl values, megaloblastic bone marrow morphology, appropriate hematologic abnormalities, and a history of alcoholism and poor diet. The samples in the Cbl-deficient infrequently treated group were from patients with pernicious anemia who were previously diagnosed as Cbl deficient as described above, but who received only intermittent treatment with parenteral Cbl at intervals of 6–9 months due to poor compliance or as part of other studies of Cbl requirements. They had low, borderline, or normal levels for serum Cbl, lacked hematologic and neurologic abnormalities, and were asymptomatic at the time the samples were collected. Serum Cbl levels were assayed using the *Lactobacillus leichmannii* method [see, e.g., Matthews, D. M. Clin. Science 22:101(1962)]or a number of radiodilution assays utilizing purified intrinsic factor or gastric juice with more than 95% of Cbl binding activity due to intrinsic factor [Kolhouse, J. F., H. Kondo, N. C. Allen, E. Podell, and R. H. Allen, N. Eng. J. Med. 299:785–792(1978)]. Serum folate was assayed with the *Lactobacillus casei* method [Goulian, M. and W. S. Beck, Am. J. Clin. Path. 46:390(1966)]or the milk binder radiodilution assay [Rothenberg, S. P., et al., N. Eng. J. Med. 286:1335 (1972)]. All of the patients' samples were coded in a manner such that the categories to which they belonged and the number of patients in each category were not known by the personnel involved in performing the methylmalonic acid and succinic acid assays.

A number of factors were examined individually for possible relationships with serum methylmalonic acid and succinic acid. For factors that were discrete, such as sex, race and diagnosis, the Wilcoxon two-sample test

[Steel, R. G. D. and J. H. Torrie, *Principles and Procedures of Statistics* (McGraw-Hill Book Co., Inc., New York, 1960]was used to determine the significance of the relation. For assessing possible relationships with neurologic severity, groups 0, 1, and 2 (as defined in Table 1) were combined and compared with combined groups 3 and 4. Factors that were continuous, such as age or mean corpuscular volume (MCV), were examined using Spearman correlative coefficients [Steel, supra]. Results are given in Table I.

TABLE I

Patient	Age	Serum Cbl pg/ml	Serum Folate ng/ml	Hct %	MCV fl	Neuro-abnormality[a]	Diagnosis[b]	Succinic Acid ng/ml	Serum MMA ng/ml
Normals		200-1000	3-23	M 40-52 F 35-47	80-100	0	0	580-2,240	19-76
1	81	115	19.3	26	135	0	0	780	22,300
2	61	68	25.5	30	108	3	PA	2,090	22,200
3	17	78	50.0*	39	109	4	IR	4,030	21,900
4	56	23	15.0	20	106	2	PA	1,890	9,500
5	68	145	50.0	39	104	3	PA	430	9,090
6	86	10	3.8	11	112	2	PA	1,670	8,300
7	64	122	50.0	18	130	3	PA	7,600	7,410
8	65	36	5.7	17	132	3	PA	1,850	6,200
9	72	17	9.7	14	111	3	PA	1,840	5,800
10	89	85	48.0	28	111	3	PA	1,730	5,790
11	31	125	14.3	38	106	3	PA	1,950	5,640
12	65	79	13.0	16	122	2	PA	4,070	5,560
13	63	60	26.0	31	117	0	PA	255	5,370
14	62	75	8.8	38	110	3	PA	2,770	4,800
15	72	110	3.4	45	101	3	PA	2,200	4,800
16	61	30	15.0	25	120	3	PA	1,235	4,580
17	64	46	26.0	19	118	0	PA	2,571	4,180
18	76	26	3.6	30	115	3	PA	2,420	3,900
19	56	132	4.7	22	98	0	PA	1,310	3,600
20	67	125	29.0	35	109	0	PA	1,780	3,350
21	72	58	>29.0	29	121	0	TS	740	2,950
22	54	50	25.0	33	117	3	PA	1,940	2,790
23	76	70	8.6	11	93	3	PA	1,610	2,740
24	17	10	28.5	12	105	0	PA	2,650	2,660
25	82	76	14.0	24	132		PA	2,190	2,500
26	47	150	11.0	31	105	3	PA	908	2,080
27	53	115	20.0	21	107	1	TS	1,270	1,990
28	92	73	4.1	41	134		PA	10,900	1,870
29	72	68	50.0*	27	106	3	MJD	1,190	1,770
30	54	62	>29.0	19	119	3	PA	2,260	1,700
31	88	130	7.0	34	135	2	PA	2,910	1,530
32	65	140	9.2	15	135	2	PA	1,030	1,530
33	69	48	19.0	20	133	2	PA	1,310	1,380
34	52	10	28.0	18	108	1	PA	1,020	1,320
35	83	150	4.3	35	113	0	PA	1,070	1,160
36	69	81	3.8	20	135	0	TS	1,560	1,160
37	22	44	3.3	16	120	1	PA	8,420	1,120
38	86	45	28.0	22	137	3	PA	460	1,100
39	61	140	5.7	18	99	0	PA	2,500	1,040
40	66	150	14.7	36	117	0	PA	1,460	751
41	58	64	6.9	18	126	1	PA	1,010	657
42	70	136		33	116	0	PA	1,430	576
43	82	135	17.0*	35	105	0	PA	2,090	526
44	66	120	2.4	15	119		PA	1,520	518
45	42	20	4.9	25	126	0	PA	2,980	465
46	80	50	6.3	38	117	2	PA	3,150	453
47	70	120	3.8	38	103	1	PA	1,340	399
48	84	66	15.8	26	118	4	PA	1,240	386
49	72	95	1.9	27	115	0	PA	2,200	352
50	80	129	3.8	35	110	0	PA	1,160	340
51	73	60	5.5	44	97	3	PA	1,761	335
52	35	30	11.0	13	110	0	PA	2,350	300
53	69	98	5.2	36	119	4	PA	1,880	273
54	59	90	1.2	14	100	0	TS	2,640	272
55	26	140	2.1	29	117	0	TS	1,120	272
56	70	130		22	126	1	PA	2,200	270
57	81	43	2.8	15	125	1	TS	1,360	231
58	83	125	10.5	43	103		PA	1,720	194
59	59	67	6.8	31	116	0	PA	2,510	170
60	72	45	41.0	42	84	4	PA	1,290	169
61	70	130	12.4	14	115	2	PA,IR	1,460	154
62	55	65	9.1	29	118	0	IR,PG	2,470	152
63	80	78		33	101	3	PA	27,900	149
64	81	16	1.2	34	80	0	PA	9,720	140
65	52	93	9.9	45	109	0	PA	1,610	139
66	41	110	5.6	29	132	0	PG	3,350	127
67	78	74	14.5	39	102	0	PA	1,660	116
68	29	74	9.7	30	108	0	PA	1,770	101
69	51	25	6.5	22	118	0	TS	490	98
70	65	66	3.6	16	116	2	TS	420	91

TABLE I-continued

Patient	Age	Serum Cbl pg/ml	Serum Folate ng/ml	Hct %	MCV fl	Serum amor mal- ties[a]	Diag- nosis[b]	Succinic Acid ng/ml	Serum MMA ng/ml
71	55	106	2.1	19	109	0	TS	1,590	61
72	70	62	2.1	27	121	0	PA	2,340	99
73	50	67	9.9	38	105	0	TS	1,840	55

[a]4 = severe advanced combined systems disease; 3 = combined systems disease or severe dysfunction responsive to Cbl treatment (Nos. 2 and 63); 2 = no neurological symptoms but impairment of position and/or vibration sense on exam; 1 = paresthesias with negative neurological exam

[b]BR = ileal resection, MJD = multiple jejunal diverticula, PA = pernicious anemia, PG = partial gastrectomy, TS = tropical sprue

[c]receiving folic acid

The values obtained for serum methylmalonic acid and succinic acid for the normal subject and patients in the various categories are shown in FIG. 6, wherein levels of serum methylmalonic acid (bottom) and serum succinic acid (top) are given for patients with clinically confirmed Cbl deficiency, folate deficiency, and Cbl-deficient infrequently treated patients who had no hematologic or neurologic abnormalities. The normal range for methylmalonic acid is 19–76 ng/ml, and 580–2420 ng/ml for succinic acid. The ranges were calculated as mean ±2 S.D. after log transformation to correct for skewness towards higher values. In the Cbl-deficient group, 69 of the 73 patients had values for methylmalonic acid that were above the normal range of 19–76 ng/ml. The highest value was 22,300 ng/ml and the median value was 1,100 ng/ml. Five of the 16 folate-deficient patients had mild elevations of serum methylmalonic acid with the highest value being 140 ng/ml. Seven of 15 samples from the Cbl deficient infrequently-treated patients who lacked hematologic and neurologic abnormalities had elevated values that ranged as high as 175 ng/ml. Of these seven samples, serum *L. leichmannii* Cbl concentrations were low (88–165 pg/ml) in six and normal (275 pg/ml) in one. All seven samples gave low Cbl values (85–155 pg/ml) with radiodilution assay using purified intrinsic factor. Of the eight samples with normal levels of methylmalonic acid; serum *L. leichmannii* Cbl was low in four.

Elevated values for serum succinic acid were observed in 19 of the 73 Cbl-deficient patients, 10 of the 16 folate-deficient patients, and 8 of the 15 Cbl-deficient infrequently treated patients. The reason for these elevations is unknown, but could be related to variations in the time that blood is allowed to stand before the serum is separated, since we have found that values for succinic acid may double when blood is allowed to stand for 24 h at room temperature before centrifugation. Values for serum methylmalonic acid do not change over this time period.

Clinical data concerning the 73 patients with Cbl deficiency are presented in Table I where they are arranged in decreasing order with respect to their serum methylmalonic acid levels. There was a significant correlation between serum methylmalonic acid and serum folate ($r=0.45$, $P<0.001$). The correlation was present in samples measured by the *L. casei* serum folate method ($r=0.46$; $P<0.01$) as well as the radioassay technique ($r=0.66$; $P<0.001$). Patients with more severe neurologic abnormalities (groups 3 and 4) had higher serum methylmalonic acid levels (mean ±SD, 5077±6073, median 3685 ng/ml) than those with milder abnormalities (groups 1 and 2, mean 2083±2866, median 879 ng/ml) or no evidence of neurological involvement (group 0, mean 1154±1468, median 409 ng/ml) ($P<0.01$ for groups 3 and 4 vs. 0–2).

Serum folate levels correlated with serum methylmalonic acid regardless of neurologic status (r for methylmalonic acid vs. folate in patients without neurologic disorders, 0.58; $n=27$; $P<0.01$). Although serum folate concentrations were higher in patients with more severe neurological abnormalities (mean serum folate in groups 3 and 4, 20.9±16.9 vs 10.1±8.7 ng/ml in groups 0–2, $P<0.005$), the association of higher serum methylmalonic acid levels with advanced neurological involvement appears to be independent of folate status. In patients with serum folate levels below 15 ng/ml, mean serum and methylmalonic acid in groups 3 and 4 was 3189±2317 ng/ml vs 1030±1795 ng/ml in groups 0–2 ($P<0.005$); serum folates did not differ significantly between the two subgroups (7.5±3.3 vs. 6.0±3.8 ng/ml, respectively, $P<0.25$).

There was a negative correlation between the platelet count and serum methylmalonic acid levels ($r=-0.30$, $P<0.05$). However, the correlation was no longer significant if patients with more severe neurologic abnormalities (groups 3 and 4) were omitted from the analysis ($r=-0.26$; $P>0.05$) or if patients with elevated serum folates were omitted ($r=-0.23$; $P>0.05$). Patients with pernicious anemia had higher values for serum methylmalonic acid (mean, 2968±4287 ng/ml) than those with tropical sprue (714±1007, $P<0.004$ using Mann-Whitney test [Steel, supra]; when corrected for the generally lower serum folate values and less severe neurologic involvement in the patients with tropical sprue, however, the difference was no longer significant. Patients with glossitis had higher serum methylmalonic acid values than patients without tongue signs or symptoms; however, 13 of the 18 patients with glossitis with serum levels of methylmalonic acid above the median for the entire group of 73 patients had severe neurologic involvement, elevated serum folate values, or both.

Serum methylmalonic acid was not correlated with serum Cbl ($r=-0.09$ for all patients; $r=0.12$ for microbiologic assay; and -0.09 for radioassays, $P>0.4$ in each instance). Serum methylmalonic acid was not significantly correlated with MCV ($r=0.07$, $P>0.05$), white blood cells ($r=-0.08$; $P>0.3$), or hematocrit ($r=-0.12$; $P>0.4$). All of the 12 patients with normal hematocrits had elevated serum methylmalonic acid levels (range 116–4800 ng/ml). There was no correlation between serum methylmalonic acid and age, sex, race, duration of symptoms, extent of weight loss, or serum levels of iron, lactate dehydrogenase (LDH), bilirubin, or albumin.

Four patients with untreated Cbl deficiency (Nos. 70–73, Table I) had serum methylmalonic acid levels within the normal range. Three had tropical sprue. One

of the four had impaired proprioception and vibration sense without neurological symptoms. There were no clinical or laboratory features that differentiated these patients from those with elevated serum methylmalonic acid concentrations.

Values for serum succinic acid did not correlate with any of the parameters studied, including serum methylmalonic acid, and significant differences were not observed between any of the various subgroups.

FIG. 7 shows sequential levels of serum (—·—) and urine (—o—) methylmalonic acid in a patient with classic pernicious anemia, beginning at the time of diagnosis and continuing over the first 13 days after treatment with parenteral Cbl. The patient was a 32-year old white male with pancytopenia, megaloblastic bone marrow findings, a serum Cbl value of 43 pg/ml, serum anti-intrinsic factor-blocking anti-bodies, and an abnormal Schilling test that corrected with exogenous intrinsic factor. Both values were markedly elevated before treatment, both decreased at similar rates after treatment, and both were just above the upper limit of normal on day 13. This suggests that measurements of serum and urine methylmalonic acid would correlate well with one another as diagnostic tests for Cbl deficiency, but a large number of additional patients must be studied before this can be concluded with certainty.

Table II contains data regarding a 95-year old white female in whom an elevated serum methylmalonic acid level preceded a low serum Cbl level:

TABLE II

	Normal	9/30/82	8/23/83[a]	9/13/83	9/20/84
MCV (fl)	80–100	105	104	102	94
Hgb (g/dl)	13.5–16.7	12.4	12.1	12.4	12.4
Serum Cbl (pg/ml)[b]	207–1098	237,230[c]	47		
Serum folate (ng/ml)	2.4–17.5	14.0,13.1[c]	10.0		
Anti-intrinsic factor-blocking antibodies	absent	present[c]	present		
Serum MMA (ng/ml)	19–76	269[c]	338	32	
Urine MMA (ng/mg creatinine)	810–3830	no sample	11,000	1,480	

[a]The patient started receiving monthly intramuscular injections of 1 mg CN-Cbl on 8/23/83 after the serum and urine were collected.
[b]radiodilution assay using purified intrinsic factor (>95% as the Cbl-binding protein
[c]These values were obtained on the serum sample taken 9/30/82, tested in early August 1983

In September 1982 she was asymptomatic but noted to have an MCV of 105 which led to the performance of serum Cbl and folate assays which gave normal values. This serum was stored for almost 1 year while the serum methylmalonic acid assay was being developed, and gave an elevated value of 269 ng/ml when it was finally assayed in August 1983. Repeat assays in August 1983 for serum Cbl and serum folate on the August 1982 sample were again normal, and antiintrinsic factor-blocking antibodies were assayed and found to be present. In August 1983 the patient was recalled to clinic where her MCV was essentially unchanged. The serum methylmalonic acid level was still elevated at 338 ng/ml and methylmalonic acid was elevated in the urine, but the serum Cbl level was now markedly decreased. Three weeks after receiving an injection of Cbl, serum and urine methylmalonic acid levels had fallen to within the normal range and, when rechecked a year later, the MCV was 94. No neuropsychiatric symptoms were noted at any time. A high unsaturated Cbl-binding capacity is an unlikely explanation for this patient since her white blood cell count has never (September 1982 - mid-1986) been elevated and her unsaturated Cbl-binding capacity was normal (2.1 ng/ml) just before treatment with Cbl (Aug. 23, 1983). Unfortunately, Cbl-binding capacity was not measured on the September 1982 sera.

Our studies demonstrate that the assay of methylmalonic acid in serum provides useful information in patients with Cbl deficiency. The fact that the serum methylmalonic acid level was elevated in 69 of 73 patients with clinically confirmed Cbl deficiency and in 7 of the 15 samples from the Cbl-deficient infrequently treated group who lacked hematologic or neurologic abnormalities, suggests that its sensitivity may be similar to that of the serum Cbl level, although studies of patients with borderline and low normal values for serum Cbl must be performed before a complete comparison of the two assays can be made. The fact that we have observed a patient in whom a moderate elevation of serum methylmalonic acid preceded the development of a low serum Cbl level suggests that the serum methylmalonic acid level will correctly detect Cbl deficiency in at least some patients in whom the serum Cbl level does not. Thus, it is likely that the serum methylmalonic acid assay and the serum Cbl assay will complement each other, and that using both assays will make it possible to define the true incidence of Cbl deficiency in various patient populations in a more thorough manner than would be possible with either test alone. The specificity of the serum methylmalonic acid assay for Cbl deficiency may prove to be greater than that of the serum Cbl level, which is frequently low in patients with no clinical evidence of deficiency or of an underlying condition affecting Cbl balance. The test may also prove to be useful in the evaluation of patients with megaloblastic anemia in whom serum levels of both Cbl and folate are subnormal.

The serum methylmalonic acid level has one advantage that is not shared by the serum Cbl level in that one can treat a patient suspected of being Cbl-deficient with Cbl and observe the effect on the serum methylmalonic acid level. If such treatment results in a decrease in the serum methylmalonic acid level from the elevated to the normal range, this is strong presumptive evidence that the patient was Cbl-deficient, as was the case with the patient described in detail in this report. This advantage is not shared by the serum Cbl level, since serum levels of Cbl are essentially always elevated or at least normal after parenteral injection of Cbl, regardless of whether a patient is Cbl-deficient or not.

Mild, but significant elevations in serum methylmalonic acid were observed in 5 of 16 folate-deficient patients who had normal serum Cbl levels. Two of these five patients had hepatomegaly and/or abnormal liver function tests and three had no evidence of liver disease. Studies involving measurements of urinary methylmalonic acid have also shown mild elevations in a few patients with folate deficiency, but it is not known if this

is due to mild coincidental Cbl deficiency or to some other unknown cause. Recent studies have shown that the amount of Cbl in various tissues is insufficient to saturate both Cbl-dependent enzymes. It is possible that in folate deficiency an attempt is made to increase levels of methionine synthetase activity by increasing the amount of Cbl bound to methionine synthetase with the result that the amount of Cbl bound to L-methylmalonyl-CoA mutase is decreased, and that this in turn results in increased formation of methylmalonic acid (see FIG. 1).

Levels of serum methylmalonic acid were not correlated with levels of serum Cbl in the Cbl-deficient patient group. A correlation between Cbl levels and levels of urinary methylmalonic acid was observed previously in some studies but not in others. The failure to find correlations between serum methylmalonic acid levels and any of the hematologic parameters, except for a weak inverse correlation with platelet count, is in agreement with studies employing levels of urinary methylmalonic acid.

Previous workers, studying small numbers of patients with neurologic abnormalities, have found no correlation with urine levels of methylmalonic acid or have suggested a possible relationship. The positive correlation between serum methylmalonic acid levels and the presence of neurologic abnormalities in our large series of patients is of interest, since the biochemical mechanisms responsible for the neurologic abnormalities in Cbl deficiency are still unknown. The positive correlation between serum folate levels and serum methylmalonic acid levels has also not been noted in studies of urinary methylmalonic acid levels. This correlation could be due to the fact that patients on diets with relatively high folate contents might have fewer hematologic abnormalities, possibly resulting in a delay in the diagnosis of Cbl deficiency. The fact that values for serum folate were not positively correlated with any hematologic parameter makes this unlikely, however. It is also possible that some unknown metabolic or regulatory relationship exists between L-methylmalonyl-CoA mutase and methionine synthetase in addition to the fact that they both require Cbl for activity.

Inspection of Table I reveals that many of the cobalamin deficient patients were not anemic, or only moderately anemic, were not macrocytic or only moderately macrocytic, and did not have markedly decreased serum Cbl levels below 100 pg/ml. These observations are in disagreement with the current beliefs and teachings of experts in the medical field (see above) and will be discussed in more detail at the end of the next example

EXAMPLE VI

Use of the Assay of Total Homocysteine Alone or of the Combined Homocysteine-Methylmalonic Acid Assays in the Diagnosis and distinction of Cobalamin and Folate Deficiency

Serum samples from 78 patients with confirmed Cbl deficiency and 19 patients with confirmed folate deficiency were tested for serum Cbl and serum folate as described in Example V, for serum methylmalonic acid as described in Example IV, and serum methionine, serum cysteine and serum homocysteine as described in Example III. The results are given in Table III:

TABLE III

Patient	Age	Serum Cbl pg/ml	Serum Folate ng/ml	Hct %	MCV fl	Neuro Abnormalities[a]	Diagnosis[b]	Serum MMA ng/ml	Serum Met umol/L	Serum Total Cys umol/L	Serum Total Hcys umol/L
Normal		200-1000		M 40-52 F 35-47	80-100	0	0	19-76	14-44	174-378	7-22
Cobalamin-deficient											
1	61	68	26.0	30	108	3	PA	22,200	43	216	476
2	64	122	50.0	18	130	3	PA	7,410	24	321	399
3	68	81	3.8	20	135	0	TS	1,160	30	190	299
4	71	145	10.0	40	119	3	PA	1,711	60	449	289
5	76	26	3.6	30	115	1	PA	3,900	19	116	256
6	17	10	28.5	12	105	0	PA	2,660	28	178	251
7	61	10	15.0	25	120	3	PA	4,580	16	262	226
8	69	150	10.0	19	120	4	PA	7,449	41	319	223
9	52	10	28.0	18	108	1	PA	1,320	35	228	205
10	65	78	13.0	16	122	2	PA	5,360	41	321	198
11	67	125	29.0	35	109	0	PA	3,350	116	127	196
12	78	70	8.6	11	83	3	PA	2,740	27	190	187
13	83	50	10.7	39	115	4	PA	2,220	34	291	187
14	56	64	8.7	18	126	3	PA	937	35	206	184
15	54	50	25.0	33	117	3	PA	2,790	21	229	183
16	56	25	15.0	20	106	2	PA	9,500	24	255	182
17	62	75	8.8	38	110	3	PA	4,800	67	210	174
18	42	20	4.8	25	126	0	PA	465	102	220	173
19	72	110	3.4	45	101	3	PA	4,600	29	330	170
20	69	85	48.0	28	111	3	PA	5,790	26	191	162
21	65	50	5.5	45	123		PA	7,470	41	348	160
22	69	44	19.0	20	113	2	PA	1,380	32	300	157
23	53	115	20.0	21	107	1	TS	1,990	38	236	153
24	56	132	4.7	22	98	0	PA	3,400	27	286	151
25	81	115	19.3	26	135		PA	22,300	33	235	150
26	68	145	90.0	36	104	3	PA	9,090	19	208	149
27	86	10	36.0	11	112	0	PA	8,300	36	240	146
28	54	62	>29.0	19	119	3	PA	1,700	34	200	140
29	65	140	9.2	16	115	2	PA	1,530	29	250	130
30	68	45	28.0	22	117	3	PA	1,100	24	126	128
31	54	65	3.9	21	111	4	PA	1,770	24	241	125
32	22	68	7.3	36	120	1	PA	1,120	42	264	126
33	69	36	5.7	17	132	2	PA	6,200	120	259	120
34	72	58	>29.0	29	121	0	TS	2,950	16	156	116

TABLE III-continued

Patient	Age	Serum Cbl pg/ml	Serum Folate ng/ml	Hct %	MCV fl	Neuro Abnormalities[a]	Diagnosis[b]	Serum MMA ng/ml	Serum Met μmol/L	Serum Total Cys μmol/L	Serum Total Hcys μmol/L
35	64	48	28.0	19	116	0	PA	4,180	120	160	117
36	28	120	32.0	31	99	0	PA	2,735	32	156	117
37	66	120	2.4	15	119		PA	518	30	351	114
38	47	150	11.0	31	109	3	PA	2,080	66	295	113
39	61	150	5.7	18	99	0	PA	1,040	38	208	113
40	51	125	14.3	38	106	3	PA	5,640	139	67	111
41	66	150	50.0	36	117	0	PA	751	18	329	109
42	92	73	4.1	41	114		PA	1,870	51	509	106
43	84	68	15.8	26	118	4	PA	386	19	348	99
44	80	50	6.3	36	115	2	PA	453	76	505	97
45	40	10	7.4	22	109	3	PA	280	37	304	97
46	88	130	7.0	34	115	2	PA	1,530	64	360	95
47	47	135	11.7	14	109	2	PA	7,605	11	168	95
48	84	130		39	99	4	PA	2,620	23	305	93
49	70	62	3.1	27	121	0	PA	59	37	230	92
50	85	43	2.8	15	125	1	TS	231	45	218	89
51	17	78	50.0*	39	109	4	IR	21,900	37	207	88
52	41	110	7.3	29	132	0	PG	137	36	106	86
53	93	150	4.3	35	113	0	PA	1,160	64	386	83
54	72	95	32.0	27	115	0	PA	352	34	270	80
55	73	60	5.5	44	97	3	PA	335	20	279	78
56	70	120	3.8	38	103	1	PA	399	28	426	76
57	35	50	11.0	13	110	0	PA	300	12	157	75
58	81	16	12.0	34	82	0	PA	149	14	398	73
59	62	10	5.2	20	112	0	PA	132	57	264	73
60	59	90	1.2	14	100	0	TS	272	64	272	73
61	65	96	7.5	16	114	2	TS	93	17	215	69
62	70	130	12.4	14	115	2	PA,IR	154	34	206	69
63	20	10	12.9	35	129	0	PA	1,656	48	210	64
64	69	98	5.2	36	119	4	PA	273	30	393	63
65	50	67	6.8	31	116	0	PA	170	32	261	60
66	70	130	8.5	27	126	1	PA	270	21	187	58
67	51	35	8.3	22	118	0	TS	78	45	198	55
68	72	45	41.0	42	84	4	PA	169	33	390	47
69	71	170	7.8	23	114	2	PA	333	16	232	45
70	70	136	3.0	33	118	0	PA	536	106	440	42
71	82	135	17.0*	25	105	0	PA	526	59	304	38
72	52	93	9.9	45	109	0	PA	139	24	273	36
73	73	150	2.9	28	105	0	PG	87	28	211	34
74	80	129	3.8	35	110	0	PA	340	84	360	32
75	29	76	5.7	30	108	0	PA	111	33	248	30
76	76	74	11.5	36	102	0	PA	116	23	224	28
77	83	125	10.5	43	103		PA	194	19	276	27
78	50	87	3.9	34	105	0	TS	55	26	163	11
Folate-deficient											
79	42	390	0.5		11	0	ALC,P	47	27	210	185
80	41	420	0.5		42	PN	ALC,P	35	59	163	134
81	59	520	0.6	32	114	0	ALC,P	79	30	238	133
82	52	3150	0.5	8	100	0	ALC,P	37	91	252	122
83	78	375	2.0	18	110	0	ALC,P	92	21	273	95
84	64	1070	1.2	25	142	0	ALC,P	53	29	326	93
85	31	425	2.3	33	114	PN	ALC,P	36	27	91	93
86	47	1160	1.1	15	108	PN	ALC,P	47	61	193	80
88	34	780	1.5	13		0	ALC,P	130	19	395	67
89	77	340	0.8	28	104	0	ALC,P	195	39	352	56
90	53	750	0.9	18	114	PN	ALC,P	152	33	281	50
91	36	1340	1.3	8	116	0	ALC,P	49	32	196	49
92	87	420	0.8	15	83	0	PD	27	20	164	49
93	37	170	0.1	13	123	0	ALC,P	109	19	137	43
94	53	370	1.0	27	112		ALC,P	73	33	179	37
95	47	200	0.1	12	122	0	ALC,P	15	56	248	36
96	46	1110	0.5	33	114	0	TS	22	18	144	26
97	26	1950	1.9	27	123	0	ALC,P	32	23	152	17

[a] 4 = severe adult-onset combined systems disease, 3 = combined systems disease or severe cerebral dysfunction responsive to Cbl treatment, no neurological symptoms but impairment of position and/or vibration sense on exam, 1 = paresthesia with negative neurological exam, PN = peripheral neuropathy associated with alcoholism.
[b] IR = ileal resection, MID = multiple jejunal diverticulitis, PA = pernicious anemia, PG = postgastrectomy, TS = tropical sprue, ALC, P = alcoholism with poor diet, PD = poor diet.
*receiving folic acid

Some, but not all, of the patients in Table III are shown in Table I also. Serum homocysteine was elevated (normal 7–22 μmol/L) in 77/78 (99%) of the patients with cobalamin deficiency and 18/19 (95%) of the patients with folate deficiency. In the cobalamin-deficient patients, serum methylmalonic acid was increased in 74/78 (95%)(normal 19–76 pg/ml). In 3 of the cobalamin-deficient patients with a normal serum methylmalonic acid level, the serum total homocysteine was elevated (range 34–93 μmol/L) and in only one patient were both the serum methylmalonic acid and serum total homocysteine within their respective nor-

mal ranges. In the folate-deficient patients, 5/19 (26%) had mild elevations of serum methylmalonic acid (range 92–195 ng/ml). Serum methionine levels were not useful in diagnosing cobalamin or folate deficiency as only 2/78 (3%) of the cobalamin-deficient patients and none of the folate-deficient patients had low levels (normal range 14–44 μmol/L). In addition, serum total cysteine levels were not useful diagnostically, since only 6/78 (8%) of the cobalamin-deficient patients had mild elevations and only 1/19 (5%) of the folate-deficient patients had an elevated value (normal range 174–378 μmol/L).

As can be seen in Table III, only 32/78 (41%) of the patients had a moderately severe anemia (Hct<25%), 28/78 (36%) had a moderate anemia (25–34% females, 25–39% males), and 18/78 (23%) were not anemic at all. Only 45/78 (58%) had a marked elevation in MCV (>110 fl), 24/78 (31%) had a mildly elevated MCV (101–110 fl), and 9/78 (11%) had a normal MCV (80–100 fl). The serum level of cobalamin was markedly decreased (<100 pg/ml) in only 48/78 (62%) patients and was only modestly (100–200 pg/ml) decreased in 30/78 (38%). Thus, the spectrum of findings in cobalamin deficiency is much broader than previously believed and one cannot rely on the findings of moderately severe anemia, a markedly depressed serum cobalamin level and a markedly increased MCV in order to make the diagnosis. However, by measuring the serum total homocysteine alone or in combination with the serum methylmalonic acid in these patients one can establish the diagnosis of cobalamin deficiency even when it is associated with mild or absent abnormalities in Hct, MCV, and serum cobalamin levels. The measurement of other amino acids such as serum methionine or total cysteine was not shown to be useful diagnostically in cobalamin deficiency, despite earlier teachings that serum methionine was low in patients with cobalamin deficiency [see, e.g., Parry, T. E., Brit. J. Haemat. 16:221(1969)]

EXAMPLE VII

Confirmation of the Diagnosis of Cobalamin Deficiency in Patients with Neurologic Abnormalities and Mild or No Hematologic Using the Assay for Homocysteine or the Combined Homocysteine-Methylmalonic Acid Assay

Neurologic abnormalities are often thought to be a late manifestation of Cbl deficiency and to occur rarely if at all in the absence of anemia or macrocytosis. To test this concept, we reviewed 143 consecutive patients with neurologic abnormalities due to CBL deficiency. We found that in 42 of these patients (29%), the hematocrit (35/42), or MCV (26/42), or both tests (19/42) were normal. Other hematologic parameters, when measured, were also frequently normal: WBC (42/42), platelets (40/42), LDH (25/38) and bilirubin (30/31). In these 42 patients, the neurologic abnormalities included distal sensory defects (35), paresthesias (29), ataxia (21), memory loss (12), personality changes (4), spastic paraparesis (3), hallucinations (2), fecal incontinence (2), obtundation (2), optic atrophy (1), and suicide (1). Serum Cbl levels (normal 200–1000 pg/ml) varied considerably as follows: <50 pg/ml (6); 50–100 pg/ml (19), 100–150 pg/ml (12); 150–200 pg/ml (3); and 200–250 pg/ml (2). The diagnosis of Cbl deficiency was confirmed in all 42 patients by demonstrating one or more of the following: a clear elevation of serum methylmalonic acid (MMA) of >150 ng/ml as measured by the procedure of Example IV, normal 18–76 ng/ml, (36/38); a clear elevation of serum homocysteine (Hcys) of >30 μmol/L as measured by the procedure of Example III, normal=7–22 μmol/L (37/38); a marked decrease in serum MMA (28/28) and serum Hcys (27/28) after Cbl treatment, a decrease of 5 fl or more in the MCV after Cbl treatment (29/35) including most patients (13/16) in whom the MCV was not elevated prior to Cbl treatment; and improvement in neurologic abnormalities after Cbl treatment (39/39).

As can be seen above, only 108 (76%) out of 143 consecutive patients with neurologic abnormalities due to cobalamin deficiency had anemia (Hct<35 female, <40 male) and 35/143 (24%) were not anemic at all. In 26 (18%) of these 143 patients, the MCV was normal and in 19/143 (13%), both the hematocrit and the MCV were normal. In the subset of 42 patients who had either a normal hematocrit, normal MCV or both, only 5/42 (12%) had a marked elevation in MCV (>10 fl), 11/42 (26%) had a mildly elevated MCV (101–110 fl), and 26/42 (62%) had a normal MCV (80–100 fl). The serum level of cobalamin was markedly decreased (<100 pg/ml) in only 24/42 (57%) patients and was only modestly decreased (100–200 pg/ml) in 16–42 (38%). In fact, 2/42 (5%) patients actually had a normal serum cobalamin level. Thus, in these patients with neurologic abnormalities resulting from cobalamin deficiency, the spectrum of hematologic abnormalities is much broader than previously realized and one cannot rely on the findings of moderately severe anemia, a markedly increased MCV, and a markedly depressed serum cobalamin level in order to make the diagnosis of cobalamin deficiency. However, by measuring the serum total homocysteine alone or in combination with the serum methylmalonic acid in these patients one can establish the diagnosis of cobalamin deficiency in patients with only mild abnormalities in Hct, MCV, and serum cobalamin levels. In addition, by monitoring the fall in elevated values of serum total homocysteine and serum methylmalonic acid, one can confirm the diagnosis of cobalamin deficiency, and one can monitor the response to treatment with cobalamin.

We conclude the following: (1) neurologic abnormalities due to Cbl deficiency occur commonly in the absence of anemia or an elevated MCV; (2) measurements of serum MMA and serum Hcys, and changes after Cbl treatment in serum MMA, serum Hcys, and the MCV are useful in evaluating patients for Cbl deficiency; (3) all patients with unexplained neurologic abnormalities should be evaluated for Cbl deficiency even if anemia, macrocytosis, or other hematologic abnormalities are not present; and (4) the clinical spectrum of cobalamin deficiency is wider than previously presumed as can be seen by the lack of anemia or elevated MCV in patients with neurologic disease secondary to cobalamin deficiency which has been confirmed by a fall in elevated serum total homocysteine or serum methylmalonic acid levels after treatment.

While we have illustrated and described the preferred embodiments of this invention, it is to be understood that this invention is capable of variation and modification, and we therefore do not wish to be limited to the precise terms set forth, but desire to avail ourselves of such changes and alternations which may be made for adapting the invention to various usages and conditions. Accordingly, such changes and alterations are properly intended to be within the full range of equivalents, and therefore within the purview, of the following claims.

We claim:

1. A method of assaying for the amount of one or more sulfhydryl amino acid species present in a given sample, said method comprising:

(a) combining said sample with an internal reference standard comprising a known amount of each sulfhydryl amino acid species to be assayed, labelled with a suitable marker;

(b) adding sufficient reducing agent to insure randomization of the labelled and unlabelled sulfhydryl amino acids present;

(c) measuring the relative amounts of labelled and unlabelled sulfhydryl amino acid present for each species with a mass spectrometer;

(d) calculating the ratio of labelled to unlabelled sulfhydryl amino acid present for each species; and

(e) deriving the amount of unlabelled sulfhydryl amino acid present for each species in said given sample.

2. The method of claim 1, wherein said labelled and unlabelled amino acids are derivatized after step (b) and before step (c).

3. The method of claim 2, wherein said derivatized amino acids are silyl derivatives.

4. The method of claim 3, wherein said silyl derivatives are obtained by exposing said amino acids to N-methyl-N-(t-butyldimethylsilyl)trifluoro- acetamide.

5. The method of claim 1 or 2 wherein said given sample comprises a body tissue from a warm-blooded animal.

6. The method of claim 5, comprising the additional step of partially purifying the sulfhydryl-containing amino acid after step (b) and before step (c).

7. The method of claim 5 wherein said sulfhydryl-containing amino acid is homocysteine.

8. The method of claim 7 wherein said internal reference standard comprises a known amount of deuterated homocysteine.

9. The method of claim 8, comprising the additional step of partially purifying the homocysteine after step (b) and before step (c).

10. The method of claim 1, comprising the additional step of assaying concurrently for one or more nonsulfhydryl amino acids by providing a non-sulfhydryl amino acid internal reference standard in step (a), measuring the amount of labelled and unlabelled non-sulfhydryl amino acids present with a mass spectrophotometer in step (c), calculating the ratio of standard to each unlabelled non-sulfhydryl amino acids present in step (d), and deriving therefrom the amount of unlabelled non-sulfhydryl amino acid present in said given sample in step (e).

11. The method of claim 10, wherein said nonsulfhydryl amino acid is methionine.

12. The method of claim 10, wherein said non-sulfhydryl amino acid internal reference standard in step (a) is norleucine.

13. A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:

assaying a body fluid for an elevated level of total homocysteine; and

correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

14. A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of

assaying a body fluid for an elevated level of total homocysteine according to the method of claim 7; and

correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

15. The method of claim 13 wherein said assay for the presence of an elevated level of total homocysteine comprises subjecting a sample of body fluid to chromatography.

16. The method of claim 15 wherein said assay for the presence of an elevated level of total homocysteine comprises subjecting a sample of body fluid to high performance liquid chromatography with an electrochemical detector set to respond to thiol groups, and comparing the results with a standard curve to determine the amount of total homocysteine present in the original sample.

17. The method of claim 13 wherein the assay for the presence of an elevated level of total homocysteine comprises converting homocysteine present in the sample to labelled S-adenosylhomocysteine by exposure to radioactively labelled S-adenosine and S-adenosylhomocysteine hydrolase, and quantifying said labelled S-adenosylhomocysteine.

18. A method for detecting a deficiency of cobalamin, folate, or both in warm-blooded animals and distinguishing therebetween comprising assaying body fluids for the presence of elevated levels of total homocysteine and methylmalonic acid, wherein normal levels of total homocysteine indicate no cobalamin or folic acid deficiency, elevated levels of total homocysteine and methylmalonic acid indicate cobalamin deficiency, and elevated levels of total homocysteine combined with normal levels of methylmalonic acid indicate folic acid deficiency.

19. A method for detecting a deficiency of cobalamin, folate, or both in warm-blooded animals and distinguishing therebetween by assaying body fluids for the presence of elevated levels of total homocysteine and methylmalonic acid, wherein the total homocysteine assay is performed according to the method of claim 7, and wherein normal levels of total homocysteine indicate no cobalamin or folic acid deficiency, elevated levels of total homocysteine and methylmalonic acid indicate cobalamin deficiency, and elevated levels of total homocysteine combined with normal levels of methylmalonic acid indicate folic acid deficiency.

20. The method of claim 18 wherein said assay for the presence of elevated levels of total homocysteine comprises subjecting a sample of body fluid to chromatography.

21. The method of claim 20 wherein said assay for the presence of elevated levels of total homocysteine comprises subjecting a sample of body fluid to high performance liquid chromatography with an electrochemical detector set to respond to thiol groups, and comparing the results with a standard curve to determine the amount of total homocysteine present in the original sample.

22. The method of claim 18 wherein the assay for the presence of elevated levels of total homocysteine comprises converting any homocysteine present in the sample to labelled S-adenosylhomocysteine by exposure to radioactively labelled adenosine and S-adenosylhomocysteine hydrolase, and quantifying said labelled S-adenosylhomocysteine by appropriate detection means.

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23. The method of claim 18 wherein the methylmalonic acid is assayed by the process of

(a) combining a tissue sample with an internal reference standard comprising a known amount of methylmalonic acid labelled with a stable isotope marker;

(b) measuring the relative amounts of labelled and unlabelled methylmalonic acid present with a mass spectrophotometer;

(c) calculating the ratio of labelled to unlabelled methylmalonic acid present; and

(d) deriving the amount of unlabelled methylmalonic acid present in said given sample.

24. The method of claim 23 wherein said labelled and unlabelled methylmalonic acid is derivatized after step (a) and before step (b).

25. The method of claim 24, wherein said derivatized amino acids are silyl derivatives.

26. The method of claim 25, wherein said silyl derivatives are obtained by exposing said methylmalonic acid to N-methyl-N-(t-butyldimethylsilyl)trifluoroacetamide.

27. The method of claim 23 or 24 wherein said internal reference standard in step (a) comprises a known amount of deuterated methylmalonic acid.

28. The method of claim 26, comprising the additional step of partially purifying the methylmalonic acid after step (a) and before step (b).

29. A method of treating a human for cobalamin deficiency which comprises assaying at least one body tissue or fluid from said human for the presence of cobalamin deficiency according tot he method of claim 13, and administering to said human an amount of cobalamin sufficient to return the total homocysteine levels to normal.

30. A method of treating a human for cobalamin deficiency which comprises assaying at least one body tissue or fluid from said human for the presence of cobalamin deficiency according to the method of claim 18, and administering to said human an amount of cobalamin sufficient to return the total homocysteine levels to normal.

31. A method of treating a human for folic acid deficiency which comprises assaying at least one body tissue or fluid from said human for the presence of folic acid deficiency according to the method of claim 13, and administering to said human an amount of folic acid sufficient to return the total homocysteine levels to normal.

32. A method of treating a human for folic acid deficiency which comprises assaying at least one body tissue or fluid from said human for the presence of folic acid deficiency according to the method of claim 18, and administering to said human an amount of folic acid sufficient to return the total homocysteine levels to normal.

33. The method for detecting a deficiency of cobalamin or folate, as recited in claim 13, wherein said assaying comprises the step of determining total homocysteine in a human body fluid.

34. The method for detecting a deficiency of cobalamin, folate, or both, as recited in claim 18, wherein said assaying comprises the step of determining elevated levels of total homocysteine and methylmalonic acid in human body fluid.

* * * * *

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No. 04-607

In the Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS, DBA LABCORP, PETITIONER

v.

METABOLITE LABORATORIES, INC., ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

PAUL D. CLEMENT
Solicitor General
Counsel of Record

PETER D. KEISLER
Assistant Attorney General

THOMAS G. HUNGAR
Deputy Solicitor General

DARYL JOSEFFER
Assistant to the Solicitor General

ANTHONY J. STEINMEYER
JEFFREY CLAIR
Attorneys

Department of Justice
Washington, D.C. 20530-0001
(202) 514-2217

JAMES A. TOUPIN
General Counsel

JOHN M. WHEALAN
Deputy General Counsel

STEPHEN WALSH
RAYMOND T. CHEN
Associate Solicitors
Patent and Trademark Office
Alexandria, VA 22313

QUESTION PRESENTED

This Court granted the petition for a writ of certiorari limited to question three as presented in the petition, which asks: Whether a method patent setting forth an indefinite, undescribed, and non-enabling step directing a party simply to "correlat[e]" test results can validly claim a monopoly over a basic scientific relationship used in medical treatment such that any doctor necessarily infringes the patent merely by thinking about the relationship after looking at a test result.

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In the Supreme Court of the United States

No. 04-607

LABORATORY CORPORATION OF AMERICA HOLDINGS, DBA LABCORP, PETITIONER

v.

METABOLITE LABORATORIES, INC., ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

INTEREST OF THE UNITED STATES

This case concerns the written description, enablement, and definiteness requirements of the Patent Act, and the question presented might also be construed to ask whether claimed inventions that would monopolize basic scientific relationships are patentable subject matter. The United States Patent and Trademark Office (PTO), which is "responsible for the granting and issuing of patents," 35 U.S.C. 2(a)(1), has an interest in the resolution of such questions. At the invitation of the Court, the United States filed a brief as amicus curiae at the petition stage of this case.

STATEMENT

1. Deficiencies in two B vitamins, cobalamin and folate, can cause serious illnesses. Once detected, however, a deficiency can be treated with vitamin supplements. Scientific researchers at University Patents

Inc., the predecessor of respondent Competitive Technologies, Inc. (CTI), determined that elevated levels of total homocysteine, an amino acid, are closely associated with deficiencies in cobalamin or folate. The researchers applied for and received a patent on methods for assaying samples of body fluids or tissues to determine total homocysteine levels, as well as methods for diagnosing cobalamin or folate deficiency based on elevated total homocysteine levels. Pet. App. 2a-3a. The patent claim at issue here, claim 13 of United States Patent No. 4,940,658 (the '658 patent), identifies:

> A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> assaying a body fluid for an elevated level of total homocysteine; and
>
> correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

Pet. App. 3a; Supp. App. (S.A.) 30.

CTI licensed the '658 patent to respondent Metabolite Laboratories, Inc., which in turn sub-licensed the patent to the predecessor-in-interest of petitioner Laboratory Corporation of America Holdings. Physicians ordered total homocysteine assays from petitioner, which initially performed the assays under its sub-license by using an assay method set forth in the patent. In 1998, however, petitioner began using a different assay method and stopped paying royalties to Metabolite. Respondents then filed suit against petitioner for inducing patent infringement by the physicians, contributory infringement, and breach of contract. Pet. App. 3a-4a.

2. The district court submitted the case to a jury, which found claim 13 of the '658 patent valid; found petitioner liable for induced infringement, contributory infringement, and breach of contract; and found that petitioner's infringement was willful. The jury assessed damages of approximately $1 million for infringement and $3.7 million for breach of contract. The district court entered judgment based on the jury verdict, denied petitioner's motion for judgment as a matter of law, and doubled the jury's infringement award based on the finding of willfulness. See Pet. App. 3a-4a, 34a-39a. The court permanently enjoined petitioner from performing "any homocysteine-only test." *Id.* at 36a (citation omitted).

3. a. The Federal Circuit affirmed. Pet. App. 1a-27a. Noting that the parties focused "solely on * * * the correlating step" of claim 13, the court of appeals stressed that it did "not address the assaying step." *Id.* at 13a & n.1. "In essence," the court held, "'correlating' means to relate the presence of an elevated total homocysteine level to either a cobalamin or folate deficiency, or both * * *, and also to relate the absence of an elevated total homocysteine level to a deficiency in neither." *Id.* at 12a.

Because "[t]he record shows that physicians order assays and correlate the results of those assays," the court of appeals held that physicians who ordered assays from petitioner after petitioner stopped making royalty payments directly infringed the patent. Pet. App. 13a. The court further concluded that substantial evidence supports the jury's finding that petitioner intended to induce such infringement because petitioner provided total homocysteine assays to physicians and encouraged the use of such assays to detect cobalamin and folate

deficiency. *Id.* at 14a-15a. Because it upheld the finding of induced infringement, the court of appeals did not review the jury's finding of contributory infringement. *Id.* at 15a.

The court of appeals rejected petitioner's contentions that claim 13 is invalid on various grounds—*viz*, indefiniteness, lack of written description, non-enablement, anticipation, and obviousness. Pet. App. 15a-21a. Because "[a] patent issued from [PTO] bears the presumption of validity under 35 U.S.C. § 282," the court explained that "[a]n accused infringer * * * must prove patent invalidity under the clear and convincing evidentiary standard." *Id.* at 15a.

In the Federal Circuit's view, petitioner did not overcome the presumption of validity. Because claim 13 has a discernible meaning, the court held that it is not indefinite. Pet. App. 16a. The court concluded that the patent specification provides an adequate written description because "[t]he record is replete with evidentiary support that * * * persons of ordinary skill in the art * * * understood from the specification that the '658 patent inventors possessed the 'correlating' step at the time they filed the patent application." *Id.* at 17a.

Similarly, the court determined that the patent specification enabled the invention by disclosing all of the necessary steps. Pet. App. 17a-18a. The court explained that "the correlating step is well within the knowledge of one of skill in this art" because it is "a simple conclusion that a cobalamin/folate deficiency exists *vel non* based on the assaying step." *Id.* at 18a. And because the prior art in the record did not specifically disclose that total homocysteine is correlated with cobalamin or folate deficiency, the court further concluded that claim 13 was neither anticipated by the prior art nor obvious.

Id. at 18a-20a. Finally, the court held that the district court's injunction barring petitioner from performing "any homocysteine-only test" is not overbroad because it "simply addresses [petitioner's] specific acts constituting indirect infringement." *Id.* at 26a-27a (citation omitted).

b. Judge Schall concurred in part and dissented in part. Pet. App. 28a-33a. He "agree[d] with the majority's conclusions with respect to validity" of claim 13, but concluded that the claim is infringed only when a test reveals elevated levels of total homocysteine, not when it reveals normal or low levels. *Id.* at 28a, 30a.

SUMMARY OF ARGUMENT

The patent specification at issue here satisfies the enablement, written description, and definiteness requirements of 35 U.S.C. 112. The specification adequately enables and describes the claimed method by explaining how it works and how to perform it, and by including examples demonstrating that the patent applicants had performed the method. The claim is also sufficiently definite because its bounds are marked with precision, such that a person skilled in the art would understand whether any given method infringed the claim. Although petitioner contends (Pet. 24-25) that the specification does not adequately describe the claim's "correlating" step, the court of appeals construed that step to be "a simple conclusion that a cobalamin/folate deficiency exists *vel non* based on the assaying step." Pet. App. 18a.

Petitioner's contention (Pet. 23) that holding claim 13 valid would mean that "parties could claim patent monopolies over basic scientific facts" confuses the Section 112 disclosure and drafting requirements with the Pat-

ent Act's separate limitations on the subject matter eligible for patent protection. Although laws of nature, natural phenomena, and abstract ideas are not patentable under 35 U.S.C. 101, petitioner did not contend in the lower courts that the patent claim is invalid under Section 101. Nor does the question presented in this Court fairly include that question. Instead, the question presented, construed in light of the arguments set forth in the body of the petition and in the courts below, asserts only that a *consequence* of affirming the jury's verdict on the Section 112 issues would be to grant a monopoly over a scientific relationship. Any such consequence, however, would flow from petitioner's failure to raise a Section 101 claim, not from any error in applying Section 112.

If the Court nonetheless concludes that the question presented fairly encompasses a Section 101 challenge, a remand would be appropriate. The court of appeals' claim construction, the jury's findings, and the relief awarded all suggest that *any* use of a total homocysteine assay infringes claim 13, because doctors who review such assays can be presumed to perform mental correlations of the results with cobalamin or folate deficiencies or the absence thereof, even if they ordered the assays for a different reason. So construed, claim 13 appears impermissibly to encompass all "substantial practical application[s]" of the natural relationship that can be identified by reference to the limited record presently before the Court. *Gottschalk* v. *Benson*, 409 U.S. 63, 71-72 (1972). Because petitioner did not raise a Section 101 challenge in the lower courts, however, respondents had no opportunity to create a full record on that issue. A remand for further evidentiary proceedings would

therefore be appropriate if the Court reached the Section 101 issue.

Claim 13 also appears to be invalid as anticipated by the prior art under 35 U.S.C. 102. The court of appeals' determination that any use of a total homocysteine assay infringes the patent appears to have the effect of impermissibly removing existing assay methods from the public domain. Like the Section 101 issue, however, that question is not fairly included in the question presented.

ARGUMENT

A. THE PATENT SPECIFICATION SATISFIES THE REQUIREMENTS OF 35 U.S.C. 112 BY DESCRIBING, ENABLING, AND CLAIMING THE METHOD

The question presented asks (Pet. i) whether a patent claim "setting forth an indefinite, undescribed, and non-enabling step" is invalid. That question refers to Section 112 of the Patent Act, which requires that a patent specification contain "a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art * * * to make and use the same." 35 U.S.C. 112. Further, "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." *Ibid.*

Section 112 thus imposes three relevant requirements. First, the specification must contain a written description of the invention. Second, the specification must enable a person skilled in the art to make and use the invention. Third, the patent claim must identify with definiteness the exact scope of the claimed invention. Because the '658 patent was issued by PTO, it is "pre-

sumed valid." 35 U.S.C. 282 Petitioner's arguments under Section 112 do not overcome that presumption.

1. a. The enablement and written description requirements are related but distinct. "The enablement requirement is satisfied when one skilled in the art, after reading the specification, could practice the claimed invention without undue experimentation." *AK Steel Corp.* v. *Sollac & Ugine*, 344 F.3d 1234, 1244 (Fed. Cir. 2003); accord PTO, *Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement* (*PTO 112 Guidelines*), 66 Fed. Reg. 1099, 1103 (2001); see *Tyler* v. *City of Boston*, 74 U.S. (7 Wall.) 327, 330 (1868) (construing analogous requirement in earlier patent statute to require that a patent "state the component parts of the new manufacture claimed with clearness and precision, and not leave the person attempting to use the discovery to find it out 'by experiment'"). Enablement is an essential aspect of the basic *quid pro quo* that underlies a patent grant, because it ensures that the invention is immediately added to the storehouse of public knowledge and that the public will receive unlimited use of the invention after patent protection expires. See *Kewanee Oil Co.* v. *Bicron Corp.*, 416 U.S. 470, 480-481 (1974); *Evans* v. *Eaton*, 20 U.S. (7 Wheat.) 356, 433-434 (1822).

In addition to enabling the invention, the specification must contain a "written description of the invention," 35 U.S.C. 112, that "convey[s] to a person of skill in the art that the patentee had possession of the claimed invention at the time of the application, *i.e.*, that the patentee invented what is claimed." *LizardTech, Inc.* v. *Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005); see Pet. App. 17a; *PTO 112 Guidelines*, 66 Fed. Reg. at 1104. "An applicant shows posses-

sion of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." *PTO 112 Guidelines*, 66 Fed. Reg. at 1104. Demonstrating that an invention has been reduced to practice is one such way of showing possession, *id.* at 1104, 1107-1108 n.6, although an invention need not have been reduced to practice in order for it to be patentable, *Pfaff* v. *Wells Elec., Inc.*, 525 U.S. 55, 60-61 (1998). In addition to ensuring that the claimant has invented and possessed the claimed subject matter, the written description requirement helps to prevent inventors from later asserting that they invented more than they in fact did. See *Moba, B.V.* v. *Diamond Automation, Inc.*, 325 F.3d 1306, 1319 (Fed. Cir.), cert. denied, 540 U.S. 982 (2003); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1561, 1563 (Fed. Cir. 1991); see generally *Evans*, 20 U.S. (7 Wheat) at 434-435.

As the court of appeals explained, the enablement and written description requirements are considered from the perspective of one skilled in the art. Pet. App. 17a, 18a; see, *e.g.*, *Tilghman* v. *Proctor*, 102 U.S. 707, 728 (1880); *Loom Co.* v. *Higgins*, 105 U.S. 580, 585-586 (1881). In this case, the parties agreed, and the jury was instructed, that such a person would have "a medical degree and experience in researching the amino acid homocysteine and its relationship to diseases." Pet. App. 7a (citation omitted).

b. Especially from the perspective of such a person, the patent specification easily satisfies the enablement and written description requirements by explaining precisely how to perform the claimed method and demonstrating that the applicants had in fact performed it.

The specification explains that "[i]t has now been discovered that an elevated level of total homocysteine in tissues of warmblooded animals correlates both with cobalamin deficiency and with folic acid deficiency; an animal with elevated levels of total homocysteine is likely to have one or both deficiencies." S.A. 11. The specification goes on to disclose both how to assay for total homocysteine and how to correlate elevated levels of total homocysteine with deficiencies in the B vitamins. See, *e.g.*, S.A. 12-14.

The specification explains that "[s]uitable assays for this purpose include any assays capable of determining levels of homocysteine in body tissues, preferably body fluids." S.A. 12. Although petitioner erroneously contends (Pet. 23) that "[n]either the claim nor the specification says anything about how one is to conduct the assay," the specification describes "several different known assays suitable for use in determining levels of homocysteine in urine or blood," S.A. 12, as well as a new assay method claimed in the '658 patent, S.A. 12-14. The specification also includes two detailed examples that describe how the applicants measured homocysteine using different assay methods. See S.A. 15-20. Thus, the specification leaves no doubt that the applicants had undertaken the assay step, and it simultaneously enables others skilled in the art to undertake that step by showing them how to do so.

The same is true of the correlation step. The specification discloses that "[t]he normal range for homocysteine in human serum is from about 7 to about 22 μmol/liter, and in human urine is from about 1 to about 20 μmol/liter. Homocysteine levels above these ranges are indicative of cobalamin and/or folate deficiency; the higher the level, the stronger the indication." S.A. 14.

The specification then provides an example of tests conducted by the applicants in which total homocysteine levels were elevated above normal levels for 99% of the patients with cobalamin deficiency and 95% of those with folate deficiency. S.A. 28.

Petitioner therefore errs in contending (Pet. 24-25) that the specification does not "describe what a practitioner must do to perform the active 'correlating' step." As the court of appeals construed the claim, "[t]he correlating step is a simple conclusion that a cobalamin/ folate deficiency exists *vel non* based on the assaying step." Pet. App. 18a; see *id.* at 8a ("The claim only requires association of homocysteine levels with vitamin deficiencies. It requires no further correlation to confirm the relationship.").

Although petitioner protests (Pet. 24) that "[a]ll the patent tells a prospective practitioner is that a person with an elevated homocysteine level *may* have a vitamin deficiency," the mere fact that the claimed detecting method may not always be accurate does not render it invalid under Section 112. The written description and enablement inquiries focus on the disclosure and possession of the invention, not the extent of its utility. And notwithstanding petitioner's criticisms, moreover, the patent claim appears to have substantial utility. The court of appeals explained that the claimed method predicts cobalamin or folate deficiency "relatively accurately." Pet. App. 11a; see S.A. 28.

c. In any event, the written description and enablement issues in this case are primarily factual. This Court long ago stated that analogous requirements in the Patent Act of 1793, ch. 11, 1 Stat. 318, were "matter[s] of fact for the jury, and not of law for the decision of the Court." *Evans*, 20 U.S. (7 Wheat.) at 428.

Under the modern patent statutes, the Federal Circuit treats the adequacy of a written description as a question of fact and enablement as a question of law based on subsidiary findings of fact. *Moba*, 325 F.3d at 1319, 1321; Pet. App. 4a-5a.

Here, the jury found that the specification satisfied both the enablement and written description requirements, J.A. 396-397, the district court denied petitioner's motion for judgment as a matter of law, Pet. App. 34a-35a, and the Federal Circuit affirmed based in part on its review of the record, see, *e.g.*, *id.* at 17a ("The record is replete with evidentiary support that * * * persons of ordinary skill in the art * * * understood from the specification that the '658 patent inventors possessed the 'correlating' step."). This Court does not ordinarily disturb such fact-specific determinations, see generally *Graver Tank & Mfg. Co.* v. *Linde Air Prods. Co.*, 336 U.S. 271, 275 (1949), and there is no reason to upset the jury's verdict on the enablement and written description questions here.[1]

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[1] There is some disagreement among the Federal Circuit's decisions regarding whether the written description requirement is satisfied by evidence the inventor possessed the invention, or whether some further description of the invention may be required in some circumstances. See, *e.g.*, *Enzo Biochem, Inc.* v. *Gen-Probe Inc.*, 323 F.3d 956, 969 (Fed. Cir. 2002). PTO has interpreted the written description requirement to focus solely on possession, see *PTO 112 Guidelines*, 66 Fed. Reg. at 1102, 1104, and the Federal Circuit's recent cases appear to adopt that view, see, *e.g.*, *LizardTech*, 424 F.3d at 1345; *Pandrol USA, LP* v. *Airboss Ry. Prods., Inc.*, 424 F.3d 1161, 1165 (Fed. Cir. 2005); Pet. App. 17a. Any disagreement on that point is not relevant here, however, because the specification clearly describes the claimed method, its allegedly novel aspects, and the extent to which it differs from the prior art disclosed in the specification, and thus satisfies either standard. See S.A. 10-14; pp. 10-11, *supra*.

2. While the enablement and written description requirements focus on the content of the patent specification, the definiteness requirement directs that the patent claim must "particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention." 35 U.S.C. 112. "It has long been understood that a patent must describe the exact scope of an invention and its manufacture to 'secure to [the patentee] all to which he is entitled, [and] to apprise the public of what is still open to them.'" *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 373 (1996) (quoting *McClain* v. *Ortmayer*, 141 U.S. 419, 424 (1891)); see *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 731 (2002).

Because the patent claim defines the scope of the patent grant, *Markman*, 517 U.S. at 373, compliance with the definiteness requirement turns on whether the claim makes "[t]he limits of the patent" known. *General Elec. Co.* v. *Wabash Appliance Corp.*, 304 U.S. 364, 369 (1938); accord *United Carbon Co.* v. *Binney & Smith Co.*, 317 U.S. 228, 232, 236 (1942). In assessing definiteness, a claim must be read in light of the specification and the knowledge of a person skilled in the art. *Carnegie Steel Co.* v. *Cambria Iron Co.*, 185 U.S. 403, 432, 437 (1902). Thus, "[t]he test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification." *Miles Labs., Inc.* v. *Shandon Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993), cert. denied, 510 U.S. 1100 (1994).[2]

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[2] Although *General Electric*, *United Carbon*, and *Carnegie Steel* interpreted the definiteness requirement of the Patent Act of 1870, ch. 230, 16 Stat. 198, the modern version of Section 112 "is not materially different from the 1870 Act with regard to claiming." *Warner-Jenkinson Co.* v. *Hilton Davis Chem. Co.*, 520 U.S. 17, 26 (1997). Accord-

Especially when read by a person skilled in the art in light of the specification, claim 13 satisfies the definiteness requirement because it marks the boundaries of the patent claim with precision. The claim is infringed only if a person "assay[s] a body fluid for an elevated level of total homocysteine," and then "correlat[es] an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate." S.A. 30. Although that language is undeniably sweeping, it is not unclear. As the court of appeals held, "[t]he claim * * * provides that if the assay discloses 'an elevated level of total homocysteine,' the physician determines whether there is a cobalamin or folate deficiency by 'correlating,' i.e., comparing the elevated level with the normal homocysteine level." Pet. App. 12a (quoting S.A. 30); see p. 11, *supra*.

3. Petitioner argues (Pet. 23) that if claim 13 satisfied the enablement, written description, and definiteness requirements, "parties could claim patent monopolies over basic scientific facts rather than any novel inventions." That argument confuses the Section 112 disclosure and drafting requirements with the Patent Act's separate limitations on the subject matter eligible for patent protection. This Court has long held that under 35 U.S.C. 101, "laws of nature, natural phenomena, and abstract ideas" may not be patented. *Diamond* v. *Diehr*, 450 U.S. 175, 185 (1981). But that limitation under Section 101 is entirely separate and distinct from the requirements of Section 112. Cf. pp. 17-27, *infra*.

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ingly, those precedents apply with full force to the current definiteness requirement.

B. WHETHER THE PATENT CLAIM IS INVALID BECAUSE IT CLAIMS A LAW OF NATURE, NATURAL PHENOMENON, OR ABSTRACT IDEA IS NOT FAIRLY INCLUDED IN THE QUESTION PRESENTED

Although the patent claim as construed by the courts below may be invalid under the rule that natural phenomena may not be patented (see pp. 17-27, *infra*), that issue is not fairly included in the question presented. Under this Court's Rule 14.1(a), "[o]nly the questions set out in the petition, or fairly included therein, will be considered by the Court." The question presented here asserts (Pet. i) that the patent claim includes a step that is not sufficiently enabled, described, or definite. Although it also asks (*ibid.*) whether such a patent claim "can validly claim a monopoly over a basic scientific relationship used in medical treatment such that any doctor necessarily infringes the patent merely by thinking about the relationship after looking at a test result," that portion of the question is not fairly read as an independent assertion that claim 13 violates Section 101 by claiming unpatentable subject matter. To the contrary, that passage appears on its face to be mere argument regarding the alleged consequences of upholding the claim against petitioner's Section 112 challenge.

The body of the petition supports that interpretation. The relevant argument heading states that "A Patent That Simply Claims A Scientific 'Correlation'—Without More—Is Indefinite, Insufficiently Described, and Non-Enabling." Pet. 23 (emphasis omitted). The heading does not assert that the claim is invalid under the natural-phenomenon doctrine of Section 101. The text of the petition (Pet. 23-26) then focuses on the Section 112 issues. Although it argues (Pet. 25) that "[i]f the Federal Circuit decision is not corrected, [respondent]

CTI and others like it would improperly gain monopolies over basic scientific facts," that contention, like the corresponding portion of the question presented, appears to be argument regarding the consequences of upholding the court of appeals' Section 112 rulings—not a stand-alone claim of invalidity based on Section 101, which is not even cited in the petition.[3] Because the petition, fairly read, challenges the patent claim's validity only on grounds *other than* failure to comply with Section 101, the claim's validity under that Section is not properly before this Court. See, *e.g.*, *Yee* v. *City of Escondido*, 503 U.S. 519, 537 (1992); *Albertson's, Inc.* v. *Kirkingburg*, 527 U.S. 555, 563 n.9 (1999); see also Gov't Cert. Br. 16-17.

The absence of any Section 101 challenge from the petition is not surprising, because petitioner did not raise such a challenge in either of the lower courts, and neither of those courts addressed the issue. In the court of appeals, petitioner noted in passing that if its indefiniteness challenge were rejected, respondent CTI "would improperly gain a monopoly over a basic scientific fact rather than any novel invention of its own." Pet. Corr. C.A. Br. 41 (citing *Diehr*, 450 U.S. at 185). As in the petition, however, petitioner advanced that cursory argument solely in support of its Section 112 challenge, not as a separate ground for reversal under Section 101. See Gov't Cert. Br. 15-17.

This Court does not ordinarily review questions that were neither pressed nor passed upon below. See, *e.g.*, *Adarand Constructors, Inc.* v. *Mineta*, 534 U.S. 103, 109

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[3] That contention is also wrong for the related reason that no matter how the Section 112 issue is resolved, other litigants will retain the right, which petitioner failed to exercise below, to make a nonpatentable subject matter argument under Section 101.

(2001). Although respondents did not call the Court's attention to the waiver in their brief in opposition, they should not be faulted for failing to raise a waiver objection to an issue that was not fairly included in the question presented. Cf. Sup. Ct. R. 15.2 ("Any objection to consideration of a *question presented* * * * may be deemed waived unless called to the Court's attention in the brief in opposition.") (emphasis added). Accordingly, this case does not properly present any issue regarding the natural phenomenon doctrine.

C. THE PATENT CLAIM APPEARS TO CLAIM ALL SUBSTANTIAL PRACTICAL APPLICATIONS OF THE NATURAL RELATIONSHIP THAT ARE REVEALED BY THE LIMITED RECORD BEFORE THE COURT

If this Court were to conclude that the question presented fairly includes a challenge to the validity of claim 13 under Section 101, any such challenge would necessarily be limited to the question whether the patent impermissibly claims "a monopoly over a basic scientific relationship," Pet. i, because that is the only potentially relevant language in the question presented. As construed by the court of appeals, and on the limited record presently before the Court, claim 13 appears to run afoul of the rule that one cannot patent every "substantial practical application" of a law of nature, natural phenomenon, or abstract idea. *Gottschalk* v. *Benson*, 409 U.S. 63, 71-72 (1972). Because petitioner did not raise a Section 101 challenge in the courts below, however, respondents had no opportunity or incentive to introduce evidence on that issue in the district court, and accordingly a remand for further proceedings would be required in order to resolve that issue definitively.

1. a. The scope of patentable subject matter is generally quite broad. "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor" if the other conditions for patentability, such as novelty, non-obviousness, and the Section 112 requirements are satisfied. 35 U.S.C. 101. Thus, this Court has noted that "Congress intended statutory subject matter to 'include anything under the sun that is made by man.'" *Diehr*, 450 U.S. at 182 (quoting S. Rep. No. 1979, 82d Cong., 2d Sess. 5 (1952), and H.R. Rep. No. 1923, 82d Cong., 2d Sess. 6 (1952)).

"Excluded from such patent protection," however, are "laws of nature, natural phenomena, and abstract ideas." *Diehr*, 450 U.S. at 185; accord, *e.g.*, *Diamond* v. *Chakrabarty*, 447 U.S. 303, 309 (1980); *Parker* v. *Flook*, 437 U.S. 584, 589 (1978); *Benson*, 409 U.S. at 67-68; *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948); *Mackay Radio & Tel. Co.* v. *Radio Corp. of Am.*, 306 U.S. 86, 94 (1939). "A principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented, as no one can claim in either of them an exclusive right." *Le Roy* v. *Tatham*, 55 U.S. (14 How.) 156, 175 (1852); see *Rubber-Tip Pencil Co.* v. *Howard*, 87 U.S. (20 Wall.) 498, 507 (1874); *O'Reilly* v. *Morse*, 56 U.S. (15 How.) 62, 116 (1853). Instead, such "manifestations of laws of nature" are "part of the storehouse of knowledge," "free to all men and reserved exclusively to none." *Funk*, 333 U.S. at 130; see *Benson*, 409 U.S. at 67 ("Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work.").

Thus, "a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter" under Section 101. *Chakrabarty*, 447 U.S. at 309. "Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity." *Ibid.* Nor can one patent "a novel and useful mathematical formula," *Flook*, 437 U.S. at 585; electromagnetism or steam power, *Morse*, 56 U.S. (15 How.) at 113-114; or "[t]he qualities of * * * bacteria, * * * the heat of the sun, electricity, or the qualities of metals," *Funk*, 333 U.S. at 130; see *Le Roy*, 55 U.S. (14 How.) at 175.

b. Claim 13 *involves* such a natural phenomenon, because it asserts and relies on the existence of a naturally occurring correlation between elevated levels of total homocysteine and deficiencies in cobalamin or folate. The natural relationship between elevated total homocysteine and deficiencies in the B vitamins is an unpatentable "principle in natural philosophy or physical science," *Morse*, 56 U.S. (15 How.) at 116, just as the relationship between energy, mass, and the speed of light discovered by Einstein ($E=mc^2$), and the relationship between force of attraction, mass, and distance discovered by Newton (the law of gravity), are unpatentable natural phenomena. See *Chakrabarty*, 447 U.S. at 309. Insofar as the relationship is no more than an observable, naturally occurring fact of human physiology, it is also analogous to observations of the properties of bacterial strains and metals, which this Court has held to be unpatentable. See *Funk*, 333 U.S. at 130.

c. Determining whether claim 13 *involves* a phenomenon of nature is only the beginning of the inquiry, however, because "[i]t is now commonplace that an *application* of a law of nature or mathematical formula to

a known structure or process may well be deserving of patent protection." *Diehr*, 450 U.S. at 187; accord *Flook*, 437 U.S. at 590 ("[A] process is not unpatentable simply because it contains a law of nature."); *Benson*, 409 U.S. at 67; *Funk*, 333 U.S. at 130. "While a scientific truth, or the mathematical expression of it, is not [a] patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be." *Diehr*, 450 U.S. at 188 (quoting *Mackay*, 306 U.S. at 94).

It is also well established, however, that a patent applicant cannot validly patent a process that comprises every "substantial practical application" of a law of nature, because such a patent "would wholly pre-empt the [law of nature] and in practical effect would be a patent on the [law of nature] itself." *Benson*, 409 U.S. at 71-72; see PTO, *Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility* (*Interim Subject Matter Eligibility Guidelines*), 1300 Off. Gaz. Pat. Office 142, 146 (Nov. 22, 2005) <http://www.uspto.gov/web/patents/patog/week47/OG/TOC.htm#ref13>. That "preemption" limitation is important because without it, "a competent draftsman [could] evade the recognized limitations on the type of subject matter eligible for patent protection." *Diehr*, 450 U.S. at 192; accord *Flook*, 437 U.S. at 590, 593.

2. If the question presented raises a Section 101 issue at all, it is whether claim 13 impermissibly asserts "a monopoly over a basic scientific relationship," because that is the only potentially relevant language in the text of the question presented. Pet. i. At most, that language can be read to raise the question whether claim 13 is invalid under the preemption rationale set forth in *Benson*, on the ground that it covers all substan-

tial practical applications of the asserted natural phenomenon. That language cannot plausibly be read to include other potential challenges to the validity of the patent claim under Section 101. It does not, for example, ask whether the claim sets forth an invalid but particularized application of the natural phenomenon, as opposed to claiming the entirety of the natural phenomenon.[4]

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[4] Under any reading of the question presented, therefore, it does not encompass the question whether a process patent that includes a transformative step satisfies Section 101 when the only "inventive" aspect of the patent is a newly discovered law of nature or natural phenomenon. See Gov't Cert. Br. 11-15 (discussing that issue); see also *id.* at 7-10. As the government explained in its brief at the petition stage (*id.* at 12-14), that question turns on the extent to which this Court's decision in *Diehr* is properly understood to limit the rationale set forth in *Flook*. That issue is not raised by the question on which the Court granted certiorari, because it asks only whether a patentee "can validly claim a *monopoly* over a basic scientific relationship" (Pet. i (emphasis added)), whereas the Court emphasized in both *Diehr* and *Flook* that those cases did *not* involve monopolization of a law of nature. *Diehr*, 450 U.S. at 187 (patentees "do not seek to pre-empt the use of that equation"); *Flook*, 437 U.S. at 589-590 (patentee "does not seek to 'wholly preempt the mathematical formula'") (quoting *Benson*, 409 U.S. at 72).

If the issue were before this Court, determining whether claim 13 constitutes a valid application of the natural phenomenon would require consideration of the claim "as a whole." *Diehr*, 450 U.S. at 188; accord *Flook*, 437 U.S. at 594 & n.16. PTO has issued interim guidelines instructing its examiners to determine that if a claim, taken as a whole, "provides a transformation or reduction of an article to a different state or thing," "the claim meets the statutory requirement of 35 U.S.C. Sec. 101." *Interim Subject Matter Eligibility Guidelines*, 1300 Off. Gaz. Pat. Office at 146. Claim 13 appears to satisfy that test because the various methods of assaying for total homocysteine that are described in the record entail significant physical or chemical alteration of a sample of blood or other bodily fluid. See, *e.g.*, S.A. 15-16, Pl. Tr. Exh. 205, Def. Tr. Exhs. JP and BT (describing such methods). PTO's guide-

a. As construed by the court of appeals, claim 13 is sweeping in its scope. The Federal Circuit determined that "[t]he claim only requires association of homocysteine levels with vitamin deficiencies." Pet. App. 8a. Under that holding, "correlate" means "to relate the presence of an elevated total homocysteine level to either a cobalamin or folate deficiency, or both * * *, and also to relate the absence of an elevated total homocysteine level to a deficiency in neither." *Id.* at 12a. According to the court of appeals, "[t]he claim simply says nothing about a confirmatory step or a further correlation beyond the stated relationship." *Id.* at 8a-9a; accord *id.* at 10a. Instead, "[t]he correlating step is a simple conclusion that a cobalamin/folate deficiency exists *vel non* based on the assaying step." *Id.* at 18a. In sum, the court of appeals held that anyone who thinks about the relationship between elevated total homocysteine and cobalamin or folate deficiency after obtaining the results of a total homocysteine assay infringes the patent claim.

The claim's breadth is further underscored by the jury's findings and the relief awarded, which suggest that doctors infringe the patent claim whenever they review the results of total homocysteine assays, regardless of the purpose for which they ordered the assays. The district court instructed the jury that it should find petitioner liable for contributory infringement if, among other things, the total homocysteine assays performed by petitioner were not "capable of substantial nonin-

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lines reflect its (and the Federal Circuit's) view that *Diehr* substantially limited the *Flook* Court's holding that a claimed method must contain some inventive aspect other than a natural phenomenon in order to be patentable under Section 101. Compare *Diehr*, 450 U.S. at 188-190, with *Flook*, 437 U.S. at 592-594; see Gov't Cert. Br. 11-14.

fringing use." J.A. 379. By finding petitioner liable for contributory infringement, the jury necessarily concluded that no substantial non-infringing uses of the total homocysteine assays had been proven on the trial record.

In so concluding, the jury implicitly rejected petitioner's contention that many of the assays did not infringe because doctors ordered them for purposes other than diagnosing cobalamin or folate deficiency. Petitioner had argued that the assays were used primarily to diagnose other conditions, especially heart disease. See Pet. C.A. Br. 31-33. Respondents' witnesses countered that, whatever the motivation for the assay, it would be "malpractice" for a physician not to perform the correlation upon viewing a total homocysteine assay, and that the other conditions associated with elevated total homocysteine are treated with supplements of cobalamin or folate in any event. See Resp. C.A. Br. 32-33, 41-42, 45. The jury's verdict demonstrates that, like the court of appeals, it credited that testimony. See Pet. App. 14a (relying on testimony that "it would be malpractice for a doctor to receive a total homocysteine assay without determining cobalamin/folate deficiency").

Indeed, the jury evidently awarded damages based on *all* of the assays performed by petitioner, because it awarded the full amount requested by respondents for "all of the assays that were done." J.A. 175-176; see J.A. 396. The district court then permanently enjoined petitioner from performing "*any* homocysteine-only test, including without limitation homocysteine-only tests via [petitioner's preferred] method." Pet. App. 36a (emphasis added and citation omitted).

Although the court of appeals did not review the jury's contributory-infringement finding or damages

award, it affirmed the scope of the district court's injunction. Pet. App. 15a, 27a. The court specifically rejected petitioner's contention that "the injunction is too broad because it extends beyond the scope of the claims." *Id.* at 27a. "To the contrary," the court concluded, "the injunction simply addresses [petitioner's] specific acts constituting indirect infringement." *Ibid.* The court of appeals thereby appears to have concluded that *any* assay for total homocysteine would infringe claim 13, regardless of the reason a doctor ordered it, because any doctor reviewing a total homocysteine result would necessarily perform the correlation in his or her head.

b. In light of that broad claim construction and the jury's findings, on the record presently before the Court claim 13 appears to cover all substantial practical applications of the natural phenomenon. As has been demonstrated, however, the parties did not litigate that issue in the lower courts, and thus respondents had neither reason nor opportunity to introduce evidence to attempt to defeat a preemption challenge. Moreover, the relevance of the jury's findings on non-infringing uses for purposes of the contributory infringement issue is diluted by the fact that respondents bore the burden of proof on that issue, whereas petitioner bore the burden of proving invalidity by clear and convincing evidence. See J.A. 378, 379-380, 390.[5]

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[5] It is unclear, moreover, whether the inquiry into substantial non-infringing uses in the contributory infringement and damages contexts is the same as the inquiry into substantial practical applications for purposes of the preemption issue. It is at least conceivable, for example, that a substantial practical application could exist (and thus preclude a finding of preemption) but be irrelevant for purposes of contributory infringement and damages, because it would be a use

It is unclear, therefore, whether the record would have reflected the existence of one or more substantial practical applications of the correlation that are not covered by the patent if the preemption issue had been fully litigated below. It is possible, however, to hypothesize potential non-infringing applications that could perhaps be found to be substantial on an appropriate record.

i. Because the assay step of claim 13 is limited to assaying a "body fluid" (S.A. 30), researchers or physicians might be able to employ the correlation without infringing the patent merely by determining total homocysteine levels through a method other than an assay of body fluids. The specification states that "[i]t has now been discovered that an elevated level of total homocysteine in *tissues* of warmblooded animals correlates both with cobalamin deficiency and with folic acid deficiency." S.A. 11 (emphasis added). The specification further explains that "[s]uitable assays for this purpose include any assays capable of determining levels of homocysteine in body *tissues*, *preferably body fluids*." S.A. 12 (emphasis added).

It is unclear whether any feasible methods exist for determining homocysteine levels without assaying body fluids, or whether any such methods would constitute substantial applications of the correlation. The specification discloses "several different known assays suitable for use in determining levels of homocysteine in urine or blood," S.A. 12, but those are body fluids. The patent also claims a series of novel assay methods that are not by their terms limited to body fluids (and one of which expressly includes assays of a "body tissue"), see S.A.

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exclusively by persons other than doctors who order homocysteine assays from petitioner.

30, but the specification's examples all involve assays of body fluids, see S.A. 12-20.[6]

ii. It might also be argued that there are uses of the correlation that do not involve any measurements, and therefore are not preempted. For example, if a patient had a condition known to be associated with elevated total homocysteine and cobalamin or folate deficiency, a doctor might prescribe cobalamin or folate supplements with an eye toward both treating the vitamin deficiency and heading off potential health problems associated with elevated total homocysteine, such as heart disease.

Under the court of appeals' construction of the "correlating" step, administering cobalamin or folate supplements in such circumstances might constitute a use of the correlation that would not involve assaying for total homocysteine. If so, the question would be whether doctors engage in that thought process to such an extent that it comprises a substantial practical application of the correlation.

c. Thus, it is conceivable that, if a preemption challenge under Section 101 had been raised in the district court, the record would reflect additional information concerning the feasibility and relative significance of those or other possible non-infringing applications of the correlation asserted in claim 13. Accordingly, if this Court were to conclude that the Section 101 issue is properly presented, it should vacate and remand for

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[6] As noted above, the district court enjoined petitioner from performing "*any* homocysteine-only test," Pet. App. 36a (emphasis added and citation omitted), and the court of appeals affirmed that injunction, *id.* at 27a. See pp. 23-24, *supra*. If the only basis for rejecting a preemption challenge to claim 13 were the existence of homocysteine tests of tissues other than body fluids, the injunction would presumably have to be narrowed to exempt such tests.

further proceedings to determine whether all substantial practical applications of the correlation are claimed by the patent.[7]

3. Regardless of whether claim 13 preempts the natural phenomenon at issue here, many medical and diagnostic procedures are unquestionably patentable. For example, the first 12 claims in the '658 patent identify assay methods whose validity has never been challenged, in part because they provide novel ways of measuring substances in bodies. See S.A. 30.

Moreover, many diagnostic procedures that involve correlations may not monopolize all of the correlations' substantial practical applications. For example, claim 14 of the patent at issue here is identical to claim 13 except that it limits the assay step to assays undertaken according to a specified and novel method. See S.A. 30. Because that claim does not cover all substantial practical applications of the natural relationship—including the assays at issue in this case, which did not make use of the method identified in claim 14—its validity would not be jeopardized by a holding that claim 13 impermissibly preempts all substantial practical applications of the natural correlation.

Other patents that use the term "correlate" might also be construed to use that term more narrowly than the court of appeals construed it here. All else being

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[7] The Federal Circuit's predecessor held that *Benson* applies only to mathematical algorithms. See, *e.g.*, *In re Toma*, 575 F.2d 872, 877 (C.C.P.A. 1978). *Benson*'s rationale—that one may not patent an "idea," and that would be the practical effect of patenting all substantial practical applications of the idea, 409 U.S. at 71—refutes any attempt to cabin *Benson*'s holding to mathematical algorithms. See also *id.* at 67-69 (relying on cases involving natural phenomena other than mathematical algorithms).

equal, the more limits a claim is read to include, the more likely it is that the claim covers only some, but not all, substantial practical applications of any natural phenomena used in the claimed invention.

D. THE PATENT CLAIM IS INVALID UNDER 35 U.S.C. 102 IF IT CLAIMS ASSAY METHODS THAT WERE ALREADY INCLUDED IN THE PRIOR ART

The question presented does not ask whether claim 13 is invalid under 35 U.S.C. 102 because it was anticipated by the prior art, and that question is therefore not before this Court. We note, however, that claim 13, as construed by the court of appeals, appears to be invalid under Section 102 because the claim effectively prevents doctors from using previously known assay methods to measure total homocysteine for *any* purpose, even if the purpose was not to diagnose cobalamin or folate deficiency.

"[T]he stringent requirements for patent protection seek to assure that ideas in the public domain remain there for the free use of the public." *Aronson* v. *Quick Point Pencil Co.*, 440 U.S. 257, 262 (1979). Thus, "§ 102 of the Patent Act * * * exclud[es] ideas that are in the public domain from patent protection," *Pfaff*, 525 U.S. at 64, by generally providing that no patent may issue on an invention previously known, used, or sold in this country, 35 U.S.C. 102(a), (b). See *Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 148 (1989). That fundamental limitation on patentability is rooted in Article I, Section 8, Clause 8 of the Constitution, which this Court has construed to preclude "the issuance of patents whose effects are to remove existent knowledge from the public domain, or to restrict free access to materials already available." *Bonito Boats*, 489 U.S. at 146

(quoting *Graham* v. *John Deere Co.*, 383 U.S. 1, 6 (1966)).

Although the court of appeals held that the prior art in the record did not specifically disclose the *correlation* between elevated total homocysteine and cobalamin or folate deficiency, Pet. App. 18a-20a, the patent specification acknowledges that methods of *assaying* for total homocysteine were known in the prior art and were used to screen for various medical conditions other than cobalamin or folate deficiency, see S.A. 12; p. 10, *supra*. As explained above, however, the lower courts enjoined petitioner from performing "any homocysteine-only test," Pet. App. 36a, and construed claim 13 in such a way that a doctor reviewing a total homocysteine assay cannot help but infringe the patent regardless of the purpose for which he or she ordered the assay. See pp. 22-24, *supra*.

So construed, claim 13 appears to remove methods of assaying for total homocysteine from the public domain, in violation of Section 102. "[I]f granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated, regardless of whether it also covers subject matter not in the prior art." *Atlas Powder Co.* v. *Ireco Inc.*, 190 F.3d 1342, 1346 (Fed. Cir. 1999); accord *Schering Corp.* v. *Geneva Pharm., Inc.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003). Although claim 13 might not be invalid as anticipated if the correlating step were construed to be less sweeping, or if the assay step were limited to novel assay methods, as construed by the

court of appeals the claim appears to remove the prior art from the public domain, in violation of Section 102.[8]

If the patent claim were held invalid, an anticipation rationale would be more administrable than a preemption rationale because it would rely on publicly known inventions, as opposed to requiring an inquiry into potential alternative applications that may not yet have been disclosed or discovered.

CONCLUSION

If this Court concludes that the question presented does not fairly include the question whether the patent claims all substantial practical applications of the natural correlation, the judgment of the court of appeals should be affirmed, or in the alternative the writ of certiorari should be dismissed as improvidently granted. If this Court concludes that the question presented does include that issue, the judgment of the court of appeals should be vacated and the case remanded for further proceedings.

Respectfully submitted.

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[8] The Patent Act specifies that "a new use of a known process" constitutes a "process" eligible for patent protection. 35 U.S.C. 100(b). Claim 13's apparent invalidity under Section 102 stems from its breadth, not from the mere fact that it applies known assay processes.

PAUL D. CLEMENT
Solicitor General
PETER D. KEISLER
Assistant Attorney General
THOMAS G. HUNGAR
Deputy Solicitor General
DARYL JOSEFFER
Assistant to the Solicitor General
ANTHONY J. STEINMEYER
JEFFREY CLAIR
Attorneys

JAMES A. TOUPIN
General Counsel
JOHN M. WHEALAN
Deputy General Counsel
STEPHEN WALSH
RAYMOND T. CHEN
Associate Solicitors
Patent and Trademark Office

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IN THE SUPREME COURT OF THE UNITED STATES

LABORATORY CORP. OF AMERICA HOLDINGS,

Petitioner,

v.

METABOLITE LABORATORIES, INC., *et al.*,

Respondents.

On Writ of Certiorari To The United States Court of Appeals For the Federal Circuit

BRIEF *AMICUS CURIAE* OF AARP IN SUPPORT OF PETITIONER

SARAH LOCK
BRUCE VIGNERY
AARP FOUNDATION

MICHAEL SCHUSTER
AARP
601 E Street, N.W.
Washington, DC 20049
(202) 434-2060

JOSHUA D. SARNOFF*
GLUSHKO-SAMUELSON
INTELLECTUAL
PROPERTY LAW CLINIC
WASHINGTON COLLEGE OF LAW
AMERICAN UNIVERSITY
4801 Massachusetts Ave., N.W.
Washington, DC 20016
(202) 274-4165

Counsel for *Amicus Curiae* AARP
*Counsel of Record

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STATEMENT OF INTEREST OF *AMICUS CURIAE*[1]

AARP is a nonpartisan, nonprofit membership organization of more than 35 million people, age 50 or older, dedicated to addressing the needs and interests of older Americans. AARP works to foster the health and economic security of individuals as they age, and to ensure access to high quality and economical health care. Older people are susceptible to vascular disease, cognitive dysfunction, and cancer, diseases associated with elevated homocysteine levels in the body.

Patents that claim the mental process of recognizing a medical phenomenon of nature leally prohibit diagnosis and treatment, and discourage communication of medical information. In light of the significance of the issues presented in this case, AARP respectfully submits this brief *amicus curiae* urging the Court to find that such patents are invalid and to clarify the limits of indirect liability.

SUMMARY OF ARGUMENT

The patent in this case improperly claims the mental process of recognizing a phenomenon of nature. The lower courts held a diagnostic test provider indirectly liable for inducing infringement based on physicians ordering and reviewing the results of an unpatented diagnostic test and then

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[1] In compliance with Rule 37.6 of this Court, *amicus curiae* AARP states that no counsel for any party authored this brief in whole or in part, and that no party or entity other than this *amicus curiae*, its members or its counsel made a monetary contribution to the preparation or submission of this brief. Counsel for AARP gratefully acknowledge the assistance of Glushko-Samuelson Intellectual Property Law Clinic students Gabriel Groisman and Cynthia Lan. Written consent of the parties has been obtained and will be filed with the Clerk of the Court pursuant to Supreme Court Rule 37.3.

recognizing the probability that a patient has a medical condition. Direct infringement should not result for physicians who cannot avoid mentally recognizing the correlation when they order the unpatented test for previously known uses. Nor should indirect liability be based on the acts of communicating knowledge of this medical phenomena or of communicating knowledge of or performing a previously known and unpatented test. The lower courts' injunction also improperly removed the test from the public domain.

This patent and others like it threaten public health by preventing patients and physicians from performing and providing needed diagnostic procedures and treatments. Such patents, and the indirect liability that may be associated with them, discourage patients, physicians, and others from communicating medical knowledge, and thus from discovering the need for medical diagnosis and treatment.

Patents have never been allowed to claim laws of nature, natural phenomena, or mental processes because scientific knowledge is not subject to proprietary ownership. Nor do such basic mental processes become patentable by adding insignificant physical steps. The claim at issue here is thus invalid, and Congress never authorized it.

ARGUMENT

I. A Diagnostic Test Provider Was Held Indirectly Liable Based on Physicians Recognizing the Probability that a Patient Has a Medical Condition.

This case involves a patent that claims the mental process of recognizing a phenomenon of nature, *i.e.*, the statistical correlation between elevated levels of homocysteine (an amino acid) in blood or urine and the condition of having

a vitamin B deficiency. U.S. Patent No. 4,940,658, Claim 13, issued July 10, 1990 ("'658 patent"). Through overly broad construction of the patent claim and the evidence, the lower courts found that physicians directly infringed the patent by thinking about this relationship whenever they ordered or reviewed unpatented total homocysteine tests that had been previously used to diagnose and treat diseases. Through expansive interpretation of the law of indirect liability, the lower courts may have found a diagnostic company liable merely for communicating the existence of this statistical correlation to physicians and for encouraging and subsequently performing the unpatented diagnostic tests. The lower courts, moreover, enjoined any and all use of the unpatented diagnostic tests. Currently, the diagnostic company cannot perform these unpatented tests and physicians and patients cannot use them without a license to diagnose or treat known diseases.[2] Through these holdings, the lower courts have impermissibly withdrawn the unpatented diagnostic tests and their previously known uses from the public domain. *See Graham v. John Deere Co.*, 383 U.S. 1, 6 (1966) ("Congress may not authorize . . . patents whose effects are to remove existent knowledge from the public domain, or to restrict free access to materials already available.")

A. The Purported Invention Is the Mental Process of Recognizing a Statistical Correlation Between a Measurement and a Medical Condition.

The '658 patent summarizes the "invention" as the

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[2] The patentee has chosen to expressly or impliedly license Claim 13 when licensing its patented homocysteine tests. Otherwise, no one could legally perform the diagnostic test.

> discover[y] that an elevated level of total homocysteine in tissues of warm blooded animals correlates both with cobalamin deficiency and with folic acid deficiency; an animal with elevated levels of total homocysteine is likely to have one or both deficiencies, but the assay does not distinguish between the two.

'658 Patent at col. 4, lines 17-23 (emphasis added).[3] The text of the claim at issue, Claim 13, reads in its entirety:

> 13. A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of: assaying a body fluid for an elevated level of total homocysteine; and correlating an elevated level of homocysteine in said body fluid with a deficiency of cobalamin or folate.

Id. (emphasis added). Claim 13 is not limited to any particular method of or equipment for assaying or correlating.

The term "assay" is defined as "1. Test of purity; trial. 2. To examine; to subject to analysis. 3. The quantitative or qualitative evaluation of a substance for impurities, toxicity, etc.; the results of such an evaluation." *Stedman's Concise Medical Dictionary for the Health Professions* 81 (4th ed. 2001). The '658 Patent explains that "assaying" involves the physical step of "quantifying sulfhydryl amino acid concentrations in a sample," which for Claim 13 means

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[3] Separately claimed methods of measuring total homocysteine are not at issue. This discovery may not have been new. *See, e.g.*, Gloria Bucco, *Dialog with the Experts: Kilmer McCully, M.D., Connects Homocysteine and Heart Disease*, Nutrition Science News (July 1999) available at www.newhope.com/nutritionsciencenews/NSN_backs/jul_99/dialogue.cfm (last visited Dec. 21, 2005).

"quantifying total homocysteine concentrations in samples of body tissue from a warm-blooded animal." '658 Patent at col. 1, lines 9-13.

The '658 patent itself recognizes that "several different [previously] known assays suitable for use in determining levels of total homocysteine in urine or blood" already exist, but asserts that their use "to detect cobalamin or folic acid deficiency" was not previously known. '658 Patent at col. 6, lines 6-9.[4] The patent and the medical literature recognize that many previously known uses of total homocysteine assays in diagnosing and treating diseases exist, such as diagnosing heart disease and monitoring drug treatments for homocystinuria. *See* '658 Patent at col. 6, lines 14-16 and 33-39; Helga Refsum, Sveln Helland & Per M. Ueland, *Radioenzymatic Determination of Homocysteine in Plasma and Urine*, 31 Clinical Chem. 624, 624 (1985).

The patent does not define "correlating" or an "elevated level," although it does recite "normal" ranges of blood and urine total homocysteine values in humans and states that "levels above these ranges are indicative of cobalamin and/or folate deficiency; the higher the level, the stronger the indication." '658 Patent at col. 9, lines 23-29. To "correlate" is "1. To put or bring into causal, complimentary, parallel, or reciprocal relation. 2. To establish or demonstrate as having a correlation." *The American Heritage Dictionary of the English Language* 299 (1981). The claim by its own terms thus does not require a determination that any individual whose blood or urine was assayed in fact has a cobalamin or folate

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[4] Although the assaying equipment used in this case was developed after the patent, and is itself unpatented, Claim 13 applies to any unpatented total homocysteine assay. *See, e.g.*, Petition for Writ of Certiorari, *Laboratory Corp. of America Holdings v. Metabolite Labs., Inc.*, No. 04-607, at 4-6.

deficiency.[5] *See* District Court Order of Nov. 29, 2000, at 2, JA 59 (the invention as a whole claims the mental process of "'determining the existence of'" a deficiency ... although not necessarily "with 100% accuracy.") *Cf. Metabolite Labs., Inc. v. Laboratory Corp. of America Holdings*, 370 F.3d 1354, 1364 (Fed. Cir. 2004) ("the claim language does not require a confirmatory step linking these conditions to diagnosed or apparent symptoms.")

The correlating step is to be performed (according to one of the inventors) by mental recognition of the existence of the statistical association.

> The physician takes the value that's been determined by the assay and then based on everything the physician knows about the patient, he or she establishes a mutual relationship between an elevated value ... if the physician thinks the value is elevated for an individual patient and a deficiency of cobalamin or folate, or if the physician believes that for a particular patient the value is not elevated, then that physician in their mind establishes that there is not a deficiency of cobalamin or folate.

Trial Tr. at 980-81, JA 140-41. *See id.* at 507, 981, JA 111, JA 141 (correlating is "all done in the mind.") Claim 13 thus seeks to patent the mental process of recognizing a phenomenon of

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[5] The claim does not require that the "elevated level" is to be determined with reference to a normal value specific to the particular animal whose blood or urine was assayed. *See* Trial Tr. at 493, JA 109. Further, the correlating step does not require use of a previously measured "elevated level" when determining that a correlation exists between an elevated level and and a deficiency for that type of body fluid. Rather, the claim uses the indefinite article "an" in the correlating step, suggesting that a different "elevated level" is to be employed.

nature, *i.e.*, the statistical risk of a vitamin deficiency for any particular homocysteine concentration in body fluid, once the fluid has been assayed for its total homocysteine content.

B. Physicians Were Found To Directly Infringe By Ordering or Reviewing Unpatented Assays and Then Recognizing The Statistical Correlation.

The District Court granted summary judgment that Laboratory Corporation of America Holdings ("LabCorp") did not directly infringe the patent. LabCorp did not perform the '658 patent's correlating step, even though LabCorp performed the assays and knew of elevated levels and of the correlation between those levels and vitamin deficiency. At trial, the jury found LabCorp liable for indirect infringement. 370 F.3d at 1354. The jury found that LabCorp induced direct infringement under 35 U.S.C. § 271(b) and contributed to infringement under 35 U.S.C. § 271(c).[6] The Court of Appeals affirmed the holding of inducing infringement but declined to address the contributory infringement issue. The necessary prerequisite for such indirect infringement liability is the direct infringement by another. *See, e.g., Joy Techs., Inc. v. Flakt, Inc.*, 6 F.3d 770, 774 (Fed. Cir. 1993). Thus, the jury impliedly found that physicians directly infringed by performing the patented process.

However, there was no direct evidence at trial that any physician performed both the step of assaying homocysteine levels and the step of correlating the results with a vitamin deficiency. There was no evidence that any physician measured

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[6] LabCorp contested the sufficiency of the evidence as to these holdings. *See* Corrected Brief for Appellant Laboratory Corporation of America Holdings, *Metabolite Labs.*, at 23-36 (Fed. Cir.) ("LabCorp App. Brief").

homocysteine levels themselves. *See Metabolite Labs.*, 370 F.3d at 1364 n.1 (not reaching the meaning of or evidence for the assaying step). The finding thus must have been premised on interpreting the assaying step to require only ordering or receiving the results of assays, or on treating LabCorp as the physicians' agents. *See, e.g., Cross Medical Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1311 (Fed. Cir. 2005) (direct liability requires the defendant or its agents to perform all steps of the process). If direct liability was based only on ordering or reviewing the test, then this interpretation of the claim contradicts the meaning of "assaying" described in the patent's specification.

Nor was there direct evidence that any physician performed the "correlating" step. The Court of Appeals upheld the implicit finding of direct infringement on the basis of circumstantial evidence that physicians had performed the correlating step. 370 F.3d at 1364-65. The District Court construed that step to require only mentally determining an "elevated" level of homocysteine — *i.e*, a level "above the normal range" for the relevant type of animal's body fluid — and "establish[ing] a mutual or reciprocal relationship between" the elevated level and a deficiency of cobalamin or folate. District Court Order of Nov. 29, 2000, at 2-3, JA 59-60. Under this construction, the jury could have found that physicians directly infringed simply by thinking about the statistical correlation for any particular elevated value in response to reading LabCorp's (or anyone else's) medical publication, so long as some total homocysteine assays had previously been ordered or received by physicians. In fact, the jury could have found that physicans directly infringed by ordering the assays and using them for an entirely different and long-standing medical purpose, so long as they incidentally thought about the statistical correlation of any measured value to cobalamin or folate deficiency.

Significantly, the jury verdict on damages assumes that all of the physicians ordered unpatented assays to determine a deficiency or unavoidably performed the correlation when using the assay for other purposes. LabCorp challenged the award for lack of evidence that every physician who received assay results performed the correlation, as there was no evidence that all physicians knew of the correlation or intended to perform it. *See* Memorandum in Support of Laboratory Corporation of America Holding's Renewed Motion for Judgment as a Matter of Law ("JMOL Motion") at 6-8. *Cf. Metabolite Labs.*, 370 F.3d at 1364 (citing testimony that "it would be malpractice for a physician to receive a total homocysteine assay without determining cobalamin/folate deficiency.") If sustained, the award would indicate that the patent itself would convert physicians' long-practiced medical procedures into unavoidable infringements, based on physicians' inevitable mental recognition of the statistical correlation that the patent itself disclosed. The patent thus would impermissibly withdraw previously known medical technology and medical knowledge from the public domain. *See Graham*, at 6.

But even if Claim 13 were restricted to intentionally performing the correlation in regard to actual values for patients obtained from assays performed by physicians, the patent would prohibit physicians from practicing good medicine without a patent license. Congress has previously precluded patent claims and remedies against physicians and related health care entities that perform or induce the "performance of a medical activity." 35 U.S.C. § 287(c)(1). The physician exception does not apply in this case, because it is only applicable to patents filed after Sept. 30, 1996, whereas this patent was filed Nov. 20, 1986. 35 U.S.C. § 287(c)(4). Although physicians were not sued here, physicians performing a process claimed by a patent filed after 1996 would not be

clearly immunized from patent infringement liability. The statute defines "medical activity" as "performance of a medical or surgical procedure on a body." 35 U.S.C. § 287(c)(2)(A). Although taking blood may constitute such a procedure, requesting a patient to provide a urine sample, ordering an assay for the sample, and reviewing and correlating the assay results all may not. And even if physicians are themselves immune from claims and remedies, their conduct can still constitute direct infringement that may form the basis for the liability of patients and of others who encourage or assist the practice of medicine, like LabCorp in this case.

C. Indirect Infringement Should Not Be Proven By Evidence of Communicating the Patent's Own Medical Disclosure or of Performing Unpatented Assays.

The jury was instructed that to find inducement liability LabCorp must have "actively and knowingly aided and abetted that direct infringement ... [and] knew or should have known that its actions would induce actual infringement." Trial Tr. at 1829. *Compare Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469 (Fed. Cir. 1990) (actual intent to induce the act that constitutes direct infringement is required) *with Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 553 (Fed. Cir. 1990) (constructive or actual knowledge required that the induced act constitutes a direct infringement). The jury was also told, however, that it could find inducement if LabCorp "provided instructions and directions to perform the infringing act through labels, advertising and other sales methods" or "by supplying the components that are used in an infringing method or apparatus with the knowledge and intent that its customers would directly infringe by using the components to make, use, or sell the patented invention." Trial Tr. at 1830 (emphasis added). Such instructions were improper

where the patent claims a new method of recognizing a natural phenomenon using previously known measuring equipment.

These improper instructions may have resulted in LabCorp being found to have induced infringement without the requisite conduct or intent. The unpatented assays purchased and performed by LabCorp and knowledge of their other uses were already in the public domain. Thus, to find liability, the jury could have based its inducement verdict on impermissible grounds, either on the act of communicating what the patent itself disclosed or on the act of communicating the assays' results.[7] *See Metabolite Labs.*, 370 F.3d at 1365 (stating that a reasonable jury could find inducement merely from publishing information that "advocate[s] use of the assay to identify a need for cobalamin/folate supplements."). Alternatively, and just as improperly, the jury could have found indirect infringement based solely or primarily on the service of performing the unpatented assays for previously known uses with knowledge that correlation to a cobalamin or folate deficiency might be performed. *See Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003) ("where a product has substantial noninfringing uses, intent to induce infringement cannot be inferred even when the defendant has actual knowledge that some users of its product may be infringing the patent.")

There were three categories of evidence purporting to establish that LabCorp aided and abetted infringing activity with requisite intent to induce infringement. These were: medical publications and advertisements that recited the

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[7] Either of these bases raises serious First Amendment concerns. *See, e.g., Washington Legal Foundation v. Henney*, 202 F.3d 331, 332-36 (D.C. Cir. 2000) (noting First Amendment concerns raised by regulatory guidelines that prohibited dissemination of certain "off-label" medical information).

existence of the correlation between homocysteine and cobalamin or folate deficiency (which inherently provided a reason for physicians to order assays and to perform the correlation); medical publications and advertisements that recited the existence of the unpatented assays and various unpatented uses of the assay results (which inherently provided a reason for physicians to order assays that might also be used to perform the correlation by physicians who know of it); and actually performing the unpatented assays (which inherently provided assistance to physicians who might perform the correlation if they knew of it). If such evidence is itself sufficient to prove inducement, it will extend liability to an absurd extent and will threaten public health even more seriously than just preventing the particular diagnostic test from being performed.[8] Nor should such evidence result in contributory infringement liability.

1. Disseminating Medical Information In the Patent's Own Disclosure Or The Prior Art Should Not Be Grounds For Virtually Unlimited Inducement Liability.

Medical publications and advertisements that merely disclose a newly discovered correlation do not aid and abet infringement any more than does publication of the patent's disclosure itself. Broad dissemination of the information contained in a patent is the central premise of granting patent

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[8] Because such evidence inherently encourages proper medical treatment, it should be considered irrelevant to inducing infringing conduct with improper intent and should be excluded under Fed. R. Evid. 401. Because juries are likely to give improper weight when considering other evidence of acts and intent to encourage infringement, it should also be deemed unduly prejudicial under Fed. R. Evid. 403.

rights.[9] Moreover, when a patent discloses and claims the mental process of recognizing a medical phenomenon, broad dissemination of the patent's disclosure is necessary to promote public health and should be a primary public policy.

However, the decision below not only serves to thwart the exchange of knowledge, it fails to establish any reasonable limitation on liability for dissemination of the information. For example, nothing in the jury instructions or in the Court of Appeals' reasoning required LabCorp to profit from the encouragement to perform the patented process provided by its medical publications or advertisements, and nothing in the law of inducement liability imposes such a requirement.[10] Thus, the inducement standard applied below would improperly extend liability to all people who seek to disseminate medical (and other scientific) information disclosed by such a patent, even though they lack any connection to the direct infringer and any pecuniary interest in the patented process.

Further, nothing in the jury instructions or in the Court of Appeals' reasoning limited evidence of inducement to publications or advertisements that specifically aided and abetted (and reflected an intent to encourage) the unauthorized

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[9] *See, e.g., Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 150-51 (1989) (" patent system thus embodies a carefully crafted bargain for encouraging the creation and disclosure of new, useful, and nonobvious advances in technology and design in return for the exclusive right.") *See generally* Malla Pollack, *What is Congress Supposed to Promote?: Defining "Progress" in Article I, § 8, Clause 8 of the United States Constitution, or Introducing the Progress Clause*, 80 Neb. L. Rev. 754 (2001).

[10] In contrast, such profit is the hallmark of vicarious liability. *See Metro-Goldwyn-Mayer Studios, Inc. v. Grokster, Ltd.*, 125 S.Ct. 2764, 2767 (2005) (one "infringes vicariously by profiting from direct infringement while declining to exercise a right to stop or limit it.").

performance of a patented process. Inducement liability does not and should not extend to assisting and encouraging use of the patented process with indifference to whether third parties will infringe (even knowing that some may).[11] The alternative would prevent dissemination of the medical knowledge disclosed by patents, and would prevent physicians from recommending medical procedures to their patients.

Similarly, medical publications and advertisements disclosing existing uses for and offering to perform unpatented diagnostic technologies should not be the basis for inducement liability. To do so would permit the grant of a patent to prohibit public discussion of technology already within the public domain. *See Graham*, 383 U.S. at 6.

2. Performing Unpatented Medical Procedures Should Not Be Grounds For Virtually Unlimited Inducement Liability.

Actually performing unpatented and previously known medical procedures also should not be the basis for inducement liability, even knowing that the results may be used to infringe a patented process. To do so would impermissibly withdraw those procedures and their results from the public domain.

Even if this outcome were permissible, it would be impractical. To avoid such liability, companies or individuals that perform the assaying step would have to police the

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[11] *See Metro-Goldwyn-Mayer Studios*, 125 S.Ct. at 2779; *id.* at 2782 n.13. Particularly in regard to patents such as the one at issue, the Court should narrow its overly broad dicta in *Metro-Goldwyn-Mayer Studios* that "active steps ... such as advertising an infringing use or instructing how to engage in an infringing use, show an affirmative intent that the product be used to infringe." 125 S.Ct. at 2779 (emphasis added). *See Warner-Lambert Co.*, 316 F.3d at 1365.

thoughts of patients and physicians who would receive the assay results. Simply warning patients and physicians not to perform the correlation without a license may not suffice to avoid inducement liability.

3. Performing Unpatented Medical Procedures Should Not Be Grounds For Virtually Unlimited Contributory Liability.

The jury verdict that LabCorp contributed to infringement also raises serious concerns about the scope of potential liability.[12] The verdict was challenged below because there were substantial non-infringing uses of the unpatented assays and because the assays were not especially adapted for infringing uses. *See, e.g.*, JMOL Motion at 8-10; LabCorp App. Brief at 31-34. Because the Federal Circuit did not address the issue, the contributory liability verdict still stands.

The provision against contributory patent infringement, 35 U.S. C. § 271(c), however, prohibits only selling or offering to sell "a material or apparatus for use in practicing a patented process...." Although Abbott Laboratories might be found to contribute to infringement by selling total homocysteine assaying equipment, LabCorp sold only the service of assaying, which is neither a "material" nor an "apparatus." Further, total homocysteine assays and their uses to diagnose and treat various disease conditions were admittedly part of the prior art. Thus, the verdict must be premised on the patent's own disclosure having eliminated all of the prior art assays' "substantial non-infringing use[s]" and having rendered all

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[12] Physicians and related medical companies that perform such unpatented assays for other physicians or for patients clearly are not immunized from contributory infringement liability, because § 287(c)(1) does not reference § 271(c).

such assays "especially adapted for use in an infringement." 35 U.S.C. § 271(c). Therefore, the contributory liability holding also impermissibly withdraws the unpatented assays and their prior art uses from the public domain.

D. The Injunction Impermissibly Prohibits All Previously Known Uses of Unpatented Assays and Immediately Threatens Public Health.

As a result of the inducement and contributory liability verdicts, the lower courts enjoined performance of all prior art uses of the unpatented prior art total homocysteine assays. *See* 370 F.3d at 1371-72 (prohibiting "any homocysteine-only test.") Not only does this injunction impermissibly withdraw those assays and their previously known uses from the public domain, it immediately threatens the public health of countless patients who otherwise might learn if they suffer from various diseases or who may need to use those assays as part of their medical regimen. *See Graham*, 383 U.S. at 6.

It is impossible to imagine an injunction for such a patent that would not be overly broad. Once the statistical correlation has become common knowledge, physicians have multiple reasons to order the prior art assays. An injunction prohibiting assaying only where the primary or sole purpose is to determine cobalamin or folate deficiency would be unworkable. An injunction prohibiting assaying only for physicians who know of the correlation also would be unworkable. Even if so limited, the injunction would threaten public health by requiring a license to diagnose and treat a known medical condition based on the newly discovered natural correlation to the prior art assay results.

II. Patents for Mental Processes of Recognizing Natural Phenomena Threaten Public Health and Interfere With the Practice of Medicine.

This patent, and any other patent that would claim the mental process of recognizing natural phenomena, threatens public health and interferes with the practice of medicine. The patent prevents the practice of existing medical procedures using previously known and unpatented medical technology and knowledge, and taxes the use of such technology to obtain the benefits of a new medical discovery. Furthermore, the threat of indirect liability associated with the patent discourages communication regarding the medical discovery and the need to perform diagnostic and treatment procedures. As a result, the practice of medicine suffers.

A. Patients Who Might Directly Infringe May Forego Diagnosis and Treatment.

Like the physicians discussed above, patients who learn of the correlation between total homocysteine and vitamin deficiency are unable to avoid practicing the patented process if they order or obtain the results of total homocysteine assays. Unlike physicians, patients are not immune from direct infringement for their own activities. Nor do patients enjoy immunity if they induce infringement by physicians. In addition, physicians may act as the agents of their patients when they unilaterally or at their patients' request perform the patented process. Patients thus may be held directly liable based on the acts of their physicians, notwithstanding § 287(c).

Patients and physicians can no longer reasonably assume that they will not be sued for infringement. *Cf.* Recording Industry Association of America, *Frequently Asked*

Questions About The Recording Industry's Use of John Doe Lawsuits, at http://www.riaa.com/news/newsletter/012104_faq.asp (last visited Dec. 14, 2005) (discussing hundreds of law suits filed against individuals for alleged copyright infringement). Rather than face potential liability, patients and physicians may instead avoid requesting unpatented total homocysteine assays. As a result, patients not only will fail to discover vitamin deficiencies, but they will fail to learn important information that they previously and routinely would have obtained from assays, such as diagnostic indications of heart disease and treatment information for known conditions.

If Claim 13 is upheld, moreover, additional patents will ensue that claim correlations of measured conditions to the risk of diseases. Such patents will force patients and physicians to obtain licenses in order to legally learn how new medical discoveries apply to their particular cases. Such licenses impose a tax on practicing the medical discovery, burdening the delivery and raising the costs of medical services. As these costs rise, public health is diminished.

Additional patents claiming the mental process of recognizing natural medical phenomena are particularly likely to threaten public health if the initial assays can be performed using simple diagnostic tests. *See, e.g., National Survey: Consumer Enthusiasm for Home Diagnostic Tests; Advanced Care (TM) Cholesterol Test Creates New Category in $1 Billion Market*, PR Newswire, June 29, 1994 ("6 out of 10 American households have used a home medical test.") For example, a new discovery that pregnancy is statistically correlated with a risk of a disease might lead to a patent claiming use of home pregnancy tests to diagnose the likelihood of the disease. Assessing pregnancy with knowledge of the correlation would result in direct liability under the lower courts' logic in this case, and the grant of the patent and

dissemination of its teaching would convert such non-infringing pregnancy assessments into unavoidable infringements. As a result, patients could be directly liable for patent infringement when using the test merely by thinking about what the results mean for their health – an absurd result not consistent with the development of rational patent or public health policy, and likely to discourage home or office medical testing rather than promote it.

B. Patients, Physicians, and Others Who Might Indirectly Infringe Will Stop Communicating About the Need for Diagnosis and Treatment.

Patients, physicians, and others may be found to induce infringement under the excessively broad standards applied below simply for disseminating information about the existence of the correlation or the availability of unpatented assays. Like LabCorp, patients who encourage physicians to order or to obtain the results of total homocysteine assays could be held liable for inducing infringement. Physicians (who benefit economically from performing medical procedures) may be held liable for inducing infringement by performing assays or offering to do so, and by informing their patients of the existence of the correlation.

To avoid liability, patients may not inform their family, friends, or physicians of the newly discovered medical phenomena or of the consequent need for diagnosis and treatment. Patients also may not help others to purchase diagnostic equipment or to perform any of the unpatented steps of the patented process. Similarly, physicians may not inform their patients, their colleagues, or the public at large of critical medical information.

As a result of potential inducement liability, medical and scientific journal publishers, the news media, medical and scientific membership organizations, diagnostic equipment and medical treatment suppliers, etc., may refuse to disseminate information about new medical discoveries that are the basis for patented processes. Patients and physicians currently rely on each other and on these third parties to learn of new medical discoveries. *See, e.g.*, K. K. Grandage, et al., *When less is more: a practical approach to searching for evidence-based answers,* 90 J. Med. Lib. Assoc. 298 (2002); J.A. Oheroff, et al., *Physicians' information needs: analysis of questions posed during clinical teaching,* 114 Annals of Internal Med. 576 (1991). Even if patients and physicians learned of new options for diagnosis and treatment from the patents themselves, they may be unable to obtain needed diagnostic and treatment supplies or services, because such suppliers may face indirect liability for patent infringement.

The result of these constraints on communication and medical services will predictably be a dramatic decrease in the level of public awareness and in the quality of medical care. The patent system was never intended to retard medical and scientific progress in this manner.

III. The Court Should Invalidate Claim 13 Because It Improperly Claims a Mental Process of Recognizing a Phenomenon of Nature.

This Court has consistently recognized that not all processes are patentable. Scientific knowledge -- including laws of nature, natural phenomena, and mental processes -- is free from proprietary ownership. Furthermore, patents may not be obtained on scientific knowledge or mental processes merely by adding insignificant prior or subsequent physical steps. In the present case, as the patent seeks to privatize the mental

process of recognizing a natural medical phenomenon, this Court should invalidate the patent. Adding a prior measurement step does not transform this unpatentable claim into a patentable invention.

A. Phenomena of Nature and Mental Processes Are Not Patentable.

The rationale for excluding from patentability laws of nature, natural phenomena, and mental processes rests on the "fundamental understanding that they are not the kind of 'discoveries' that the [patent] statute was enacted to protect." *Parker v. Flook*, 437 U.S. 584, 593 (1978). *See Diamond v. Diehr*, 450 U.S. 175, 185 (1981) (excluding "laws of nature, natural phenomena, and abstract ideas"); *id.* at 195 (Stevens, J., dissenting) (mental steps were unpatentable "on the familiar principle that a scientific concept or a mere idea cannot be the subject of a valid patent"). These categorical exclusions are soundly based on the idea that "[p]henomena of nature ... mental processes and abstract intellectual concepts are ... the basic tools of scientific and technological work." *Gottschalk v. Benson*, 409 U.S. 63, 68 (1972) (emphasis added). *See Funk Bros. Seed Co. v. Kalo*, 333 U.S. 127, 130 (1948) ("manifestations of laws of nature [are] free to all men and reserved exclusively to none"); *Flook*, 437 U.S. at 593 n.15 (patentable inventions must not be "merely heretofore unknown," to avoid depriving the public of prior uses). *Cf.* Dan L. Burk & Mark A. Lemley, *Inherency*, 47 Wm. & Mary L. Rev. 371, 383 (2005) (where the public already has the benefit of the invention, the value of providing knowledge of why the invention works does not warrant its withdrawal from the public domain).

These exclusions derive from the historic understanding that nature and science are the common heritage of mankind, free from appropriation by particular persons.[13]

> If nature has made any one thing less susceptible than all others of exclusive property, it is the action of the thinking power called an idea.... That ideas should freely spread from one to another over the globe, for the moral and mutual instruction of man, and improvement of his condition, seems to have been peculiarly and benevolently designed by nature, when she made them, like fire, expansible over all space, without lessening their density in any point....

Letter from Thomas Jefferson to Isaac McPherson (Aug. 13, 1813), in 13 *The Writings of Thomas Jefferson* 326, 333-34 (Albert Ellery Bergh ed. 1908).

This distinction of nature and science (which could not be made the subject of patents) and technological applications of natural phenomena and scientific principles (which could) was reflected in the Constitution itself. *See* U.S. Const., Art. I, Sec. 8, Cl. 8 ("To promote the Progress ... of useful Arts").[14]

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[13] *See, e.g.*, John Temple Swing, *Who Will Own the Oceans?*, 54 Foreign Aff. 527, 528 (1976) (Dutch jurist Hugo "Grotius's philosophy of 'freedom of the seas' also involved the concept of common ownership, *res communis*, an idea akin in principle to [Arvid] Pardo's 'common heritage,' enunciated three and one-half centuries later.")

[14] *See* Edward C. Walterscheid, *"Within the Limits of the Constitutional Grant": Constitutional Limitations on the Patent Power*, 9 J. Intell. Prop. L. 291, 349 (2002) ("In other words, natural phenomena, laws of nature, or abstract ideas, without more, are not considered to be 'useful arts.'"); Walterscheid, *The Preambular Argument: The Dubious Premise of Eldred v. Ashcroft*, 44 IDEA 331, 343 (2004); Noah Webster, *American Dictionary*

This Court should reaffirm that natural phenomena and scientific knowledge have not yet been withdrawn from the public domain and remain free for all to use.

Moreover, laws of nature, natural phenomena, and mental processes are unpatentable because claims to broadly applicable scientific knowledge would exceed actual inventive contributions and subsequently hinder rather than promote technological progress. *See, e.g., Le Roy v. Tatham,* 55 U.S. (14 How.) 156, 175 (1853) (patent may not claim an "effect" or "the result of a certain process" because it would prohibit other inventions that perform the same functions and discourage technological progress); *Corning v. Burden,* 56 U.S. (15 How.) 252, 268 (1853) (processes not limited to the "method or mode of producing" the desired function are unpatentable). As the seminal case of *O'Reilly v. Morse*, 56 U.S. (15 How.) 62 (1854) holds, one cannot claim all uses of a natural phenomenon for a particular purpose.

> It can hardly be supposed that under such a patent he could have prevented the use of the improved machinery which science has since introduced; although the motive power is steam, and the result is the propulsion of vessels. Neither could the man who first discovered that steam might, by a proper arrangement of machinery, be used as a motive power to grind corn or spin cotton, claim the right to the exclusive use of steam as a motive power for the purpose of producing such effects.

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of the English Language, unnumbered page headed "ARR-ARS-ART" (1st ed. 1828, reprinted in Foundation for American Christian Education (10th ed. 1998)) (defining art).

Id. at 113. *See Diehr*, 450 U.S. at 191 (unpatentability "cannot be circumvented" by limiting "use of the [mathematical] formula to a particular technological environment.")

Although the Court later allowed broad functional claims to processes that apply natural phenomena, it has neither invalidated the core holding of *O'Reilly* nor withdrawn scientific information from the public domain.[15] There remains a critical line to be drawn between unpatentable scientific principles that must remain in the public domain and the patentable applications of those principles. Likewise, the courts must distinguish between overly broad process claims that unduly burden technological progress and narrower process claims that promote it.

B. Insignificant Physical Steps Cannot Transform Unpatentable Scientific Principles or Their Recognition Into Patentable Processes.

This Court has recognized that minor physical steps cannot transform unpatentable scientific knowledge into a patentable invention. In *Flook*, the Court rejected the argument that a method including a mathematical algorithm was patentable because the information output was subsequently used to practical effect. 437 U.S. at 590. The Court reasoned:

> the notion that post-solution activity, no matter how conventional or obvious in itself, can transform an unpatentable principle into a patentable process exalts form over substance. A competent draftsman could

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[15] See, *Dolbear v. American Bell Tel. Co.*, 126 U.S. 1, 535 (1888); *Cochrane v. Deener*, 94 U.S. 780, 787-88 (1876); *Holland Furniture Co. v. Perkins Glue Co.*, 277 U.S. 245, 257 (1928); *Diehr*, 450 U.S. at 187.

> attach some form of post-solution activity to almost any mathematical formula; the Pythagorean theorem would not have been patentable, or partially patentable, because a patent application contained a final step indicating that the formula, when solved, could be usefully applied to existing techniques.

Id. (emphasis added). *Diehr* confirmed this critical holding. 450 U.S. at 192 & n.14.

Moreover, the Court in *Flook* made clear that unpatentable phenomenon of nature must be considered part of the public domain for purposes of considering both the status of the claimed invention as patentable subject matter and its novelty (or obviousness). 437 U.S. at 591-92 (citing *Benson*, 409 U.S. at 67). Significantly, the Court explicitly referenced § 101 in this context. *See id.* at 594 ("Respondent's process is unpatentable under § 101" because once the algorithm was considered part of the prior art there was "no patentable invention") (emphasis added). The Court in *Diehr* again confirmed these holdings, adding only that the old elements of the claim may not be ignored when evaluating patentable subject matter under § 101. *See* 450 U.S. at 188, 189 & n.12. Thus, courts must consider the claim "as a whole" when evaluating patentable subject matter. *Id.* at 188.

This reasoning similarly applies to processes claiming conventional or obvious pre-solution activity, such as taking initial measurements. Such measurements are required as input values to predict the operation of natural laws or to establish the results of employing a mathematical formula. Taking the measurement and predicting or calculating the result remains the performance of a natural law or a mathematical formula.

C. Claim 13 Improperly Claims The Mental Process of Recognizing a Phenomenon of Nature.

In the present case, Claim 13 of the '658 patent purports to possess the mental process of recognizing a medical phenomenon of nature. As discussed above, this patent claims recognition of the statistical correlation for any particular elevated homocysteine level after performing (or ordering or reading the results of) any prior art total homocysteine assay. Allowing the patenting of such claims contradicts this Court's precedent prohibiting patenting of scientific knowledge. Even the most limited construction of this claim involves the mental process of determining that the statistical correlation is likely to be true (*i.e.*, that a scientific fact exists) for a particular individual. This claim is thus nothing like the process of curing of synthetic rubber in *Diehr*, where the results of the mathematical algorithm had direct physical application.

There is no patentable invention in Claim 13 under § 101, in the sense intended in *Flook* and *Diehr*.[16] This claim to the unpatentable mental step of recognizing the unpatentable natural phenomenon of a statistical correlation of homocysteine with cobalamin or folate deficiency did not become patentable subject matter simply by adding the prior art assaying step to

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[16] Claim 13 also lacks sufficient inventiveness to be patentable under § 103. Knowledge of the correlation inherently suggests combination with the prior art assaying step, and thus the process is obvious. *See, e.g.*, *Teleflex, Inc. v. KSR Intern. Co.*, 119 Fed. Appx. 282, 285 (Fed. Cir.2005) (obviousness requires "suggestion, teaching, or motivation" to combine), *petition for cert. pending*, No. 04-1350. Unlike *in Dann v. Johnston*, 425 U.S. 219, 223 (1976), the Court should rule here on the § 101 grounds it certified.

the imputed prior art mental step of correlating.[17] The claimed invention remains a mental process of recognizing a natural phenomenon. Claim 13 merely limits the application of the natural phenomenon to the "particular technological environment" of an assayed fluid, which is not enough for patentability. *Diehr*, at 191.

Moreover, allowing Claim 13 to be considered patentable based on insignificant prior physical activity, *e.g.*, measurement, will lead to unreasonable results. Claim 13, and similar claims to mentally recognizing newly discovered phenomena of nature, would prohibit or chill all such measurements. With such claims patentable, the first person to have discovered that the position of the sun relative to the earth can be used to measure the time of day could have prevented people from looking at the sun. If Claim 13 is upheld, the Court will open the floodgates to such unreasonable patents, burdening science, medicine, and countless everyday activities.

D. Congress Has Not Authorized Patents for Mental Processes of Recognizing Phenomena of Nature.

When enacting 35 U.S.C. § 101 and the corresponding definition of a process in 35 U.S.C. § 100, Congress intended only to codify the existing law of patentable subject matter as the prior statute had been interpreted by this Court. Congress changed the archaic term "art" to "process," defined "process" to include "method," and clarified that a new use of a known

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[17] *Cf.* Brf. for Pet., *Dann v. Johnston*, No. 74-1033, at 34 (Solicitor General arguing no change occurred in physical identity of a computer by mentally associating a new meaning with a physical state of the computer: "[n]or does a ... computer [thereby] become a 'different machine.'")

process or of a known apparatus or composition of matter was patentable. S. Rep. No. 82-1979, at 1, 4, 6 (1952).

However, by codifying pre-existing case law, Congress clearly did not intend to extend patentable subject matter to categories of inventions previously held unpatentable.[18] The House manager for the new Act stated:

> A definition of invention in terms of discovery was included to show that this bill does not distinguish between the word 'invention' and the word 'discovery." The Department of Justice felt that this might open the door to a new era of patents and permit the creation of monopolies in some of the fundamental discoveries in the field of science. I can assure you that was not our intention. We merely intended to state the present law and remove any doubt on this subject.

98 Cong. Rec. A415 (1952) (Extension of Remarks, Hon. Joseph R. Bryson). Congress also rejected a provision that would have permitted the patenting of "a noninventive application of a newly-discovered natural principle." Brief for the Pet., *Dann v. Johnston*, No. 74-1033, at 24 n.21 (citing H.R. 9133, § 101, 81st Cong., 2d Sess. (1950)).

The contemporaneous understanding of § 101 suggests that the Patent Act preserved the prior case law on patentable subject matter, including its limitations regarding scientific

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[18] *See, e.g., In re Schraeder*, 22 F.3d 290, 295 & n.11 (Fed. Cir. 1994); *In re Tarczy-Hornoch*, 397 F.2d 856, 869 (C.C.P.A. 1968) (en banc) (Kirkpatrick, J., dissenting). *Cf. In re Alappat*, 33 F.3d 1526, 1553 n.13 (Fed. Cir. 1994) (en banc) (Archer, C.J., concurring in part and dissenting in part) ("It is erroneous ... to characterize ... nonstatutory subject matter such as a mathematical algorithm as an 'exception' to § 101.")

knowledge. *See, e.g.*, Karl B. Lutz, *The New 1952 Patent Statute*, 35 J. Pat. Off. Soc'y 155, 157 (1953) ("inventions relate to the 'useful arts' (in modern language 'practical arts') but do not 'push back the frontiers of science.'"). Following the 1952 Patent Act, this Court and various Courts of Appeals continued to hold that the previously identified categories of scientific knowledge and mental processes were unpatentable. *See, e.g., Diehr*, 450 U.S. at 185; *Tarczy-Hornoch*, 397 F.2d at 857-869 (citing cases); *Schraeder*, 22 F.3d at 295 (citing cases).

Furthermore, when enacting § 101 in 1952, Congress did not bar this Court from applying its past patentability precedents to new technologies. For example, in 1980, the Court decided that genetically-modified organisms constitute patentable subject matter. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980). But contrary to the Court's dicta, that result was not appropriately premised upon a presumed Congressional intent, in codifying § 101, for "'anything under the sun made by man'" to comprise "statutory subject matter." *Id.* at 309 (quoting S. Rep. No. 82-1979, at 5). *See, e.g.*, Malla Pollack, *Originalism, J.E.M., and the Food Supply, or Will the Real Decision Maker Please Stand Up?*, 19 J. Envtl. L. & Litig. 495, 508-09 (2004) (the purpose of the quoted legislative history was to limit not extend patentability).[19] That result was appropriate because Congress intended to preserve the Court's historic interpretive discretion.

For the legal and policy reasons previously stated, this Court should not now extend patentable subject matter to a

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[19] Even if Congress had intended such a broad change to patentability standards, that intent would have been limited to the other three classes of subject matter — machines, articles of manufacture, and compositions of matter — and would not have reflected any change to the standards for processes. A process is not "made by man" and is not any "thing."

mental process of recognizing a natural medical phenomenon. In so holding, this Court will not invalidate broad classes of patents for genetic and biotechnological materials, software, and business methods that resulted from unwarranted extensions of patentable subject matter by the lower courts and consequently by the U.S. Patent and Trademark Office. *See, e.g., State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 149 F.3d 1368 (Fed. Cir. 1998); *AT&T Corp. v. Excel Communications, Inc.*, 172 F.3d 1352 (Fed. Cir. 1999); U.S. Patent and Trademark Office, *Interim Guidelines for Examination of Patent Applications* for Patent Subject Matter Eligibility, 1300 O.G. 142 (Nov. 22, 2005). Congress has impliedly ratified most of these specific judicial expansions of patentable subject matter. *See, e.g.*, 35 U.S.C. § 103(b) (biotechnological processes); 35 U.S.C. § 273 (business methods). Reversing the decision here would also broadly invalidate lower court and agency interpretations and would constitute a regulatory taking or would interfere with important sectors of the American economy is unwarranted.

Rather, the Court should acknowledge that Congress has not encouraged further dramatic extensions of patentable subject matter, and should not unilaterally take that step. *See, e.g., Deepsouth Packing Co. v. Laitram Corp.*, 406 U.S. 518, 531 (1972) (the Court "should not expand patent rights by overruling or modifying ... prior cases construing the patent statutes.... [without] a clear and certain signal from Congress")

CONCLUSION

In order to best promote progress, protect public health, and prevent unwarranted liability, this Court should invalidate Claim 13 and clarify indirect liability standards.

December 23, 2005 Respectfully submitted,

Sarah Lenz Lock
Bruce Vignery
AARP Foundation

Michael R. Schuster
AARP
601 E Street, NW
Washington, DC 20049
(202) 434-2060

Joshua D. Sarnoff*
Glushko-Samuelson Intellectual
Property Law Clinic
Washington College of Law
American University
4801 Massachusetts Ave., NW
Washington, D.C. 20016
(202) 274-4165

Counsel for *Amicus Curiae* AARP
* Counsel of Record

(19)

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IN THE

Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS (DOING BUSINESS AS LABCORP),
Petitioner,

v.

METABOLITE LABORATORIES, INC. AND COMPETITIVE TECHNOLOGIES, INC.,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

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BRIEF FOR *AMICI CURIAE* AFFYMETRIX, INC. AND PROFESSOR JOHN H. BARTON IN SUPPORT OF PETITIONER

BARBARA A. CAULFIELD
AFFYMETRIX, INC.
3380 Central Expressway
Santa Clara, CA 95051
(408) 731-5151

KATHLEEN M. SULLIVAN
Counsel of Record
BRIAN C. CANNON
QUINN EMANUEL URQUHART OLIVER & HEDGES, LLP
555 Twin Dolphin Drive, Suite 560
Redwood Shores, CA 94065
(650) 801-5000

December 23, 2005

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INTEREST OF *AMICI CURIAE* [1]

Amicus Affymetrix, Inc. is the worldwide leader in providing commercial DNA microarrays to the scientific research community. DNA microarrays are small substrates (such as specially manufactured glass chips) on which millions of different strands of DNA are arranged in an ordered manner, allowing researchers to investigate the genetic properties of humans, plants and animals. Affymetrix DNA microarrays are called GeneChip® arrays.

Since 1994, when Affymetrix introduced the first commercial DNA microarray, microarrays have revolutionized genomic research and related applications. Customers use Affymetrix's GeneChip technologies for two central applications: gene expression monitoring and DNA variation detection. Affymetrix and its customers and collaborators develop clinical applications of GeneChip technologies for diagnosing and treating disease. The value of GeneChip technology for studying complex biosystems is demonstrated by the more than 3900 peer-reviewed publications citing GeneChip technology.

As a member of the life sciences industry, Affymetrix has an interest in ensuring that patents not issue on basic laws of nature so as to impede scientific progress in analyzing DNA and gene expression. While the patent at issue in this case involves a laboratory test, a decision whether it improperly seeks exclusive rights to a natural phenomenon also has implications for patents involving genetic sequences—patents that affect the ability of Affymetrix's customers to undertake

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[1] Counsel for both parties have consented to the filing of this brief, and their consents have been filed with the Clerk of this Court. No counsel for either party had any role in authoring this brief, and no person other than the named *Amici* and their counsel has made any monetary contribution to the preparation and submission of this brief. *See* Rule 37 & 37.6.

scientific research that will advance the capacity to understand genetic phenomena and advance new medical care.

Amicus John H. Barton is Professor of Law Emeritus at Stanford University, and is an expert in the role of patents in medicine and biotechnology. He has published extensively in both the legal and the scientific literature. He was a member of the London-based Nuffield Commission on Bioethics Roundtable which produced the July 2002 report, *The Ethics of Patenting DNA*, and of the U.S. National Research Council Committee on Intellectual Property Rights in the Knowledge-Based Economy, which produced the 2004 report, *A Patent System for the 21st Century*. He has been a Visiting Scholar in the Department of Clinical Bioethics at the National Institutes of Health, supported in part by the National Human Genome Research Institute. His interest in this case is that patent law evolve in a way that serves the public interest by supporting both scientific research and medical innovation.

SUMMARY OF ARGUMENT

The question presented in this case concerns the scope of patentable subject matter under the Patent Act of 1952. The Act provides: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title." 35 U.S.C. § 101. Although the scope of patentable subject matter is thus broad, it is settled precedent that it does not extend to natural phenomena. "Excluded from such patent protection are laws of nature, natural phenomena, and abstract ideas." *Diamond v. Diehr*, 450 U.S. 175, 185 (1981).

The patent claim in dispute in this litigation is claim 13 of United States Patent No. 4,940,658:

> 13. A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:

> assaying a body fluid for an elevated level of total homocysteine; and
>
> correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

The correlation described in this patent is a scientific fact, a law of nature, relating two phenomena in the human body. Claim 13 thus violates the settled principle that one may not patent a natural phenomenon.

In crossing over the line between patents on human invention and patents on nature itself, claim 13 upsets the "careful balance" inherent in the patent laws that is "the very lifeblood of a competitive economy." *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 146 (1989). A United States patent confers upon its owner the powerful right to exclude others from practicing whatever invention is claimed in the patent for a defined period of time. *See* 35 U.S.C. § 271 (defining infringement) and § 154 (twenty-year term). Such a right to exclude can also extend to the substantial equivalent of the patented invention. *See, e.g., Warner-Jenkinson, Inc. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 21 (1997). Such powerful rights should not be conferred upon claims on laws of nature so as to preempt the future progress of scientific research and advances in medical technology.

Allowing claim 13 to stand would damage such future research and scientific progress. Claim 13 and others like it allow no room to design around, imitate, or improve upon the so-called "invention" of a law of nature. DNA technology has opened up a vast array of tests based on naturally occurring biochemical mechanisms. But if claims like claim 13 are sustained, such tests will be blocked by patents on the law of nature on which they are based. This is especially harmful given the nature of modern genomic research, which focuses not on one gene or gene function at a time, but rather on complex interconnections among genes and gene functions.

Such interconnections cannot be studied if portions of the larger genomic map are blocked out.

By contrast, invalidating claim 13 and reaffirming the principle set forth in *Diehr* will not disrupt or impede scientific research. Contemporary patent practice is to file many claims in a single patent, some narrow, some broad, in order to maximize exclusive rights; for example, Respondent Metabolite holds and receives royalties on many of the other thirty-three claims of the '658 patent apart from claim 13. Invalidating claim 13, the broadest of these claims and an attempt to push the outer limits of patentable subject matter, will not invalidate Metabolite's patent, nor discourage Metabolite's scientific research. It will simply restore the balance between natural phenomena and human-made inventions that Congress originally sought to strike in the patent laws—a balance that reflects the Constitution and has served the patent system and the progress of science very well. The decision below should be reversed or vacated.

ARGUMENT

I. CLAIM 13 IMPROPERLY REMOVES A NATURAL PHENOMENON FROM THE PUBLIC DOMAIN

A. Patentable Subject Matter Does Not Include Laws Of Nature, Natural Phenomena, Or Abstract Ideas

Congress intended the scope of patentable subject matter to be broad and inclusive, even for technologies that had yet to be imagined. The Committee Reports accompanying the 1952 Patent Act provide that Congress intended statutory subject matter to "include anything under the sun that is made by man." S. Rep. No. 82-1979, at 5 (1952); H.R. Rep. No. 82-1923, at 6 (1952), *quoted in Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980).

But Congress likewise established just and appropriate limits to the reach of the patent statutes. The patent laws protect only *inventive* products and processes. Thus not every discovery is necessarily patentable. A bedrock principle of United States patent law is that: "Excluded from such patent protection are laws of nature, natural phenomena, and abstract ideas." *Diamond v. Diehr*, 450 U.S. 175, 185 (1981). Accordingly:

> [A] new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E = mc^2$; nor could Newton have patented the law of gravity. Such discoveries are "manifestations of . . . nature, free to all men and reserved exclusively to none."

Chakrabarty, 447 U.S. at 309 (quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)). *See Parker v. Flook*, 437 U.S. 584, 593 n.15 (1978) ("[R]ecognition of a theretofore existing phenomenon or relationship carries with it no rights to exclude others from its enjoyment."); *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972) ("Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work.").[2]

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[2] The laws of other nations and patent systems likewise preclude patenting natural phenomena and laws of nature. *See, e.g.*, European Patent Convention Article 52(2) (excluding from patentability "discoveries, scientific theories and mathematical methods"), *available at* http://european-patent-office.org/legal/epc/e/ma1.html#CVN; India, Patents Act, 1970 § 3(c) (excluding from patentability "mere discovery of a scientific principle or the formulation of an abstract theory"), *available at* http://ipindia.nic.in/ipr/patent/patAct1970-3-99.html; Japan, Examination Guidelines for Patent and Utility Model in Japan, Part II, Chapter 1 ("A law of nature as such" is "not considered to be a statutory invention.") (English translation available at Japanese Patent Office website at http:// www.jpo.go.jp/tetuzuki_e/t_tokkyo_e/1312-002_e.htm).

Whether a claimed invention is a valid subject matter for a patent under these principles has been the subject of several decisions of this Court since the 1952 Patent Act became law.[3] In several of these decisions, the Court upheld the patentability of the subject matter: In *Chakrabarty*, for example, the Court held that human-made bacteria that exhibit characteristics different from any bacteria occurring in nature are patentable subject matter. 447 U.S. at 310. In *Diehr*, the Court held that a computerized industrial process for control of a rubber curing mold is patentable, even though the process "admittedly employs a well known mathematical equation." 450 U.S. at 187. And in *J.E.M. AG Supply, Inc. v. Pioneer Hi-Bred International, Inc.*, 534 U.S. 124 (2001), the Court held that newly developed plant breeds are patentable subject matter.

In several other decisions, however, the Court held the subject matter of a patent to constitute a law of nature beyond the scope of the Act. In *Parker v. Flook*, for example, the Court held that a process for monitoring chemical reactions by using a mathematical formula is not patentable. 437 U.S. at 594. And in *Gottschalk v. Benson*, the Court held that a process related to converting decimal to binary numerals using a formula is not patentable. 409 U.S. at 71-72.

The distinction between the two lines of cases turns on whether the patentholder seeks to preempt the underlying law of nature, precluding others from testing or observing it. As the Court noted in *Diehr*, "an *application* of a law of nature . . . to a known structure or process may well be deserving of patent protection." *Diehr*, 450 U.S. at 187. The Court found

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[3] The principle that one cannot patent natural phenomena is longstanding and predates the 1952 Patent Act. *See, e.g.*, *Funk Bros. Seed Co.*, 333 U.S. at 130 ("He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes. If there is to be invention from such a discovery, it must come from the application of the law of nature to a new and useful end.").

such an application in *Diehr* because, in that case, the patent holders "do not seek to pre-empt the use of that equation" but "seek only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process." *Id.* In contrast, the Court in *Gottschalk* found no patentable subject matter where "the patent would wholly pre-empt the mathematical formula and in practical effect would be a patent on the algorithm itself." 409 U.S. at 72.

The distinction between the two lines of cases also turns, in the case of method claims like the one at issue in this case, on whether the patented process is transformative. In analyzing the patentability of a claimed process, both *Diehr* (which upheld a claimed process) and *Gottschalk* (which struck down a claimed process) focused on the *end result* of the process: "Transformation and reduction of an article 'to a different state or thing' is the clue to the patentability of a process claim that does not include particular machines." *Diehr*, 450 U.S. at 184; *see Gottschalk*, 409 U.S. at 70.

For the reasons that follow, claim 13 should be found on the non-patentable side of this well-established line because it involves no such transformation and seeks to preempt all use by others of a basic natural phenomenon.

B. Patent Claim 13 Improperly Asserts Exclusive Rights To Test And Observe A Natural Phenomenon—Namely, That Elevated Levels Of An Amino Acid In The Blood Correlate To A Vitamin Deficiency

The claim at issue in Respondents' patent in this case, claim 13 of U.S. Patent No. 4,940,658 (the '658 patent), is directed to a natural phenomenon. Claim 13 is a method claim, seeking to patent a method of determining a vitamin deficiency by testing a sample for elevated levels of an amino acid, then noticing that the level is elevated, and then correlating that fact with a vitamin deficiency. Through creative

patent drafting in the form of a process claim, claim 13 preempts the natural phenomenon by precluding all others from testing and observing this phenomenon.

To grasp how claim 13 seeks to carve out a natural phenomenon, it is useful to examine briefly its technical background: Vitamins are small, but vital compounds that assist metabolism in the human body. Many vitamins are not produced by the body but must be consumed as part of a person's diet. Metabolism is the series of chemical steps performed within the body in order to create or break down substances. For instance, proteins are formed by the amino acids combining into large chains. Each amino acid must be synthesized from building block components or consumed as part of the diet.

In the tissue of a human body, there exists a relationship between the level of a certain amino acid, homocysteine, and the level of two vitamins, B_{12} and folic acid. The amino acid homocysteine is a building block in the creation of other amino acids that are used to form proteins. The relationship between the levels of homocysteine and the vitamins exists because these two vitamins assist in the breakdown of homocysteine as part of the body's natural metabolism. It cannot be disputed that this relationship is "the handiwork of nature"—it existed long before the inventors named in the patent did their work, and nothing these inventors did changed the relationship.

Like the discoverers of a previously unknown plant in the wild, the inventors named in the '658 patent assert that they were the first to have uncovered this natural relationship:

> It has been discovered that elevated levels of homocysteine in body tissue correlate with decreased levels of cobalamin [vitamin B_{12}] and/or folic acid in said body tissue.

'658 Patent at col. 5, lines 64-66. The inventors state that this discovery arose by testing the blood of 78 patients with

known vitamin B_{12} deficiency and 19 patients with known folic acid deficiency for total homocysteine. '658 Patent at col. 36, lines 26-31. The inventors observed that elevated amounts of the amino acid correlated with the vitamin deficiency. Such basic steps of scientific inquiry—testing, observing, and drawing conclusions—can be applied to all natural phenomena.

Claim 13 seeks to exclude others from performing a two-step process:

> 13. A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> *assaying* a body fluid for an elevated level of total homocysteine; and
>
> *correlating* an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

'658 Patent at col. 41, lines 58-65 (emphasis added). An "assay" is simply a test.[4]

The significance of this claim is that the claimed "invention" is not limited to any particular kind of assay or any assay protocol. Any test infringes. Thus, infringement of this process might occur if a doctor sends a patient's blood sample to a lab to be tested for homocysteine (and perhaps other substances), and then receives the results, notices that there is an elevated level of homocysteine, and concludes that the patient may have a vitamin deficiency. In this scenario, the

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[4] *See, e.g.*, THE MERRIAM-WEBSTER DICTIONARY 56 (1974) ("n. 1: a test (as of gold) to determine characteristics (as weight or quality);" and "v. 2: to subject (as an ore or drug) to an assay"). Under Federal Circuit claim interpretation precedent, courts are free to consult dictionaries at any time to assist in the understanding of patent claims. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1322 (Fed. Cir. 2005) (*en banc*) ("[J]udges are free to consult dictionaries and technical treatises at any time in order to better understand the underlying technology and may also rely on dictionary definitions when construing claim terms.").

doctor is a direct infringer even if the doctor had no idea how the testing was done; and the lab that performed the test is liable as an indirect infringer for inducing the doctor's infringement. One may not even test one's own blood to observe the relationship without running afoul of the claim.

Claim 13 thus allows the patent holder to own a naturally occurring phenomenon—the biochemical relationship between an amino acid and a vitamin. As the lower court said, "The correlating step is a simple conclusion that a cobalamin/folate deficiency exists *vel non* based on the assaying step." Pet. App. 18a. The correlation described in this claim is a scientific fact, a law of nature, relating two phenomena in the human body.

In contrast to the patent claim upheld in *Diehr*, there are *no* other steps in the claimed process here. Claim 13 covers every substantial practical application of this law of nature. Such a claim relating the magnitude of a measured phenomenon to a correlated phenomenon is little different from one claiming a method of estimating the risk of heart attack on the basis of measurements of blood pressure. Such a patent, like claim 13, would preempt all use of a particular law of nature.

It should be beyond dispute that patent holders may not claim they own the natural biochemical relationship between an amino acid and a vitamin. That relationship exists in every tissue in every human body and other animals and pre-exists any human invention or observation. By drafting their claims in the form of a process, the patent holders have sought to erect a fence around the relationship, depriving the public of access to observation of this natural phenomenon. But creative claim drafting by patent attorneys cannot transform otherwise unpatentable subject matter into a valid invention. *See Flook*, 437 U.S. at 590; *Diehr*, 450 U.S. at 192 ("To hold otherwise would allow a competent draftsman to evade the recognized limitations on the type of subject matter eligible for patent protection.").

By way of analogy, consider the commonly known law of nature that Force = Mass x Acceleration. One obviously may not patent this law simply by putting it into patent language: "A two-step method of determining the force on an object by measuring its mass and multiplying the mass by the object's acceleration" is a claim that would certainly be invalid. Similarly, if one were to find a plant growing in the wild in some remote area, one could not patent the plant *per se* no matter how surprising or useful the plant may be. To be sure, one might patent an innovative therapy involving the plant, or methods of extraction of useful substances from the plant, or novel compositions of matter including ingredients from the plant. But the line is drawn at patenting "nature's handiwork"—the phenomenon that already existed in nature before discovery by a person. The natural relationship between homocysteine and vitamins is just such a phenomenon.

Claim 13 thus seeks to exclude from the public domain a natural phenomenon for purposes of scientific research. In the language of *Diehr* and *Gottschalk*, the natural relationship between elevated amino acid levels and vitamin deficiency has been "pre-empted" by the patent claim. Allowing Respondents to appropriate such a phenomenon of nature as their exclusive property would require departure from this Court's long-settled precedents. For the reasons that follow, upholding claim 13 would also cause serious harm to the cause of scientific research, especially in the genomic area.

II. ALLOWING CLAIM 13 WOULD UPSET THE PATENT BALANCE CAREFULLY STRUCK BY CONGRESS AND THIS COURT AND WOULD HARM FUTURE RESEARCH AND INNOVATION IN THE LIFE SCIENCES

The Constitution requires that patents "promote the Progress of Science and useful Arts." Art. I, § 8, cl. 8. Fulfilling this constitutional purpose requires a balance between rewarding existing research and ensuring that other research

may go forward freely in the future. Allowing a patentee to remove a natural phenomenon from the public sphere would thwart this constitutional purpose by impeding rather than promoting the progress of biochemical research and medical treatments. Without access to testing and observing natural phenomena, medical researchers cannot build upon the discoveries of others.

Allowing claims such as the one at issue here would block medical information based on natural, biochemical relationships from appropriate further scientific use. This impediment would be especially acute with respect to the information and phenomena that are rapidly being discovered in the field of genome analysis. Disallowing claims such as claim 13, by contrast, will cause little harm to scientific progress because a wide range of other appropriate claims would remain available to researchers like Respondent. Thus the balance struck in *Diehr* and related cases on the scope of patentable subject matter should be preserved.

A. Existing Limitations On The Scope Of Patentable Subject Matter Reflect A Careful Balance Between Rewarding Existing Research And Ensuring Opportunity For Future Innovation

Patents are fundamentally a balance between allowing free competition and government-granted exclusive rights. "The Patent Clause itself reflects a balance between the need to encourage innovation and the avoidance of monopolies which stifle competition without any concomitant advance in the 'Progress of Science and useful Arts.'" *Eldred v. Ashcroft*, 537 U.S. 186, 215 (2003) (citing *Bonito Boats*, 489 U.S. at 146). *See Mazer v. Stein*, 347 U.S. 201, 219 (1954) (noting that the patent system is based upon the "conviction that encouragement of individual effort by personal gain is the best way to advance public welfare through the talents of authors and inventors").

Patent law pervasively seeks to strike a balance between these competing interests. Some features of patent law ensure adequate returns to the large fixed costs of research and development. For example, Congress has decided upon a twenty-year term for patents. *See* 35 U.S.C. § 154. And by denying an independent creation defense to patent infringement, this Court has permitted liability to attach even if a person has no knowledge of the patent. *See Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 477 (1974). Other features of patent law seek to preserve opportunities for future innovation. For example, there is a statutory safe harbor for activities that would otherwise constitute patent infringement if they are undertaken for purposes reasonably related to the development and submission of information under a federal law that regulates drugs. 35 U.S.C. § 271(e); *Merck KGAA v. Integra Lifesciences, Ltd.*, 125 S. Ct. 2372 (2005) (exemption applies to preclinical research); *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990) (exemption applies to medical devices).

The definition of what constitutes patentable subject matter likewise reflects a balance that has been struck by Congress in section 101 of the Patent Act and by this Court in interpreting that section. This balance—which distinguishes between natural phenomena and human-made inventions—has served the United States patent system and the progress of science in the nation very well.

The key to this balance is the recognition that there are interests in promoting innovation on *both* sides of any patent. As this Court stated in a different context in *Bonito Boats*, "[f]rom their inception, the federal patent laws have embodied a careful balance between the need to promote innovation and the recognition that imitation and refinement through imitation are both necessary to invention itself and the very lifeblood of a competitive economy." 489 U.S. at 146. As Justice Breyer has noted in the related context of copyright

law, in ensuring a balance between preserving incentives to intellectual property holders and protecting opportunities for others to develop new technologies, it is important to be sure that "the gains on the copyright swings would exceed the losses on the technology roundabouts." *Metro-Goldwyn-Mayer Studios, Inc. v. Grokster, Ltd.*, 125 S. Ct. 2764, 2793 (2005) (Breyer, J., concurring).

Here, allowing claims like claim 13 would cause serious "losses on the technology roundabouts," upsetting the balance that Congress and this Court have long struck with respect to patenting laws of nature. By precluding scientific inquiry (*i.e.*, the ability to test, observe and conclude) into naturally occurring phenomena, claim 13 and others like it have and will remove the common tools accessible to all scientists that allow scientific progress to be made. Invalidating claim 13, by contrast, would still allow wide berth for patenting truly transformative human inventions that add to rather than subtract from the public domain.

B. Allowing Claim 13 To Stand Would Impede Future Biomedical And Genetic Research That Depends Upon Common Access To Natural Phenomena

Science has always proceeded in an incremental way in which one discovery builds upon another. Experts in the scientific method have accordingly noted that scientific progress requires that research results be open for all to "use, attempt to replicate, and evaluate."[5] This aspect of scientific progress would be impeded if patents could extend to natural

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[5] U.S. National Research Council Committee on Intellectual Property Rights in the Knowledge-Based Economy, A PATENT SYSTEM FOR THE 21ST CENTURY 26 (2004) (citing Robert K. Merton, THE SOCIOLOGY OF SCIENCE: THEORETICAL AND EMPIRICAL INVESTIGATIONS (1973)).

phenomena. The Council of the [United Kingdom] Royal Society recently drew a parallel implication:

> [P]ure knowledge about the physical world should not be patentable under any circumstances. That it should be freely available to all is one of the fundamental principles of the culture of science. Only by having knowledge unencumbered by property rights can the scientific community disseminate information and take science forward.[6]

Whatever the effect of the scope of patentability on scientific research in the past, however, these principles are even more important to the next generation of biomedical and genetic research. The nature of the information contained within the genetic code presents new and unique incentives to try to own natural phenomena. Any holding that one may effectively own a natural biochemical relationship by excluding others from any and all testing of that relationship thus would have especially fundamental implications for future research in the field of DNA and human genetic conditions.[7]

The human genetic code is contained in twenty-three pairs of chromosomes, which are present in almost every cell of the human body. These chromosomes are passed on from generation to generation. The chromosomes comprise tightly wound bundles of the long, thin molecule DNA. Along its length, DNA contains a sequence of four compounds called bases. This sequence is a code that is the template for protein production in all cells. Every individual (except identical twins) has a slightly different sequence.

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[6] Royal Society Working Group on Intellectual Property, KEEPING SCIENCE OPEN: THE EFFECTS OF INTELLECTUAL PROPERTY POLICY ON THE CONDUCT OF SCIENCE 8 (April 2003).

[7] The scope of preemption is significant, for it has been estimated that approximately one-fifth of all human genes are already patented. Kyle Jensen & Fiona Murray, *Intellectual Property Landscape of the Human Genome*, 310 Science 239 (2005).

The biochemical relationships among an individual's DNA, the individual functional units (called "genes"), the expression of proteins, and the resulting physical manifestation of these processes in the human body are the subject of intense scientific research. Once the genetic code was discovered, researchers quickly developed tools to investigate the relationships between specific portions of DNA and their impact on the physical condition. These tools include databases of the precise sequence of human DNA, databases of differences among different persons' DNA, and testing kits that allow comparison of one person's DNA to another's.

If claim 13 were allowed to stand, all such naturally occurring biochemical relationships would be subject to ownership rights on the part of the person who discovers them. For instance, it has been discovered over the last generation of genomic medicine that mutations in a single gene may be associated with hereditary diseases or abnormalities in particular body structures. Thus, one common form of a natural relationship might be: a mutation in the DNA at point "X" is related to the physical condition "Y." Under an approach like claim 13's, the first person to discover this relationship could claim the following in a patent: a method of determining condition "Y," by testing for mutation "X" and correlating the presence of mutation "X" with condition "Y."

A claim like claim 13 might thus preclude a person from testing her own genetic code. Yet testing for a relationship between a single gene mutation and a physical condition has demonstrated medical value and may even be life saving. For example, Affymetrix's GeneChip® technologies were recently involved in path-breaking discoveries about two very serious childhood diseases observed disproportionately in the Amish population. One involved a particular type of sudden infant death syndrome; the other a set of crippling neurological diseases. Affymetrix provided a chip that enabled ready detection of the presence or absence of a large number of

"SNPs" or "single nucleotide polymorphisms" in a human tissue sample. SNPs are single-base variations, places in which different persons' genes differ in just one nucleic acid. They have been mapped across the whole human genome and can be used as markers to locate the portion of the genetic code contributing to a particular disease or condition. Using Affymetrix chips, researchers' work with twenty-one persons over sixty days made it possible to identify the gene mutations that were correlated with a form of sudden infant death syndrome.[8] The patenting of SNPs despite their existence as natural phenomena would greatly complicate such research efforts.[9]

The impediments to genetic research if natural genetic phenomena were allowed to be patented are compounded by the fact that modern genomic research has moved past such one mutation/one function examples to explore much more complex interrelationships among genes and genetic functions.[10]

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[8] *See* E.G. Puffenberger et al., *Mapping of Sudden Infant Death with Dysgenesis of the Testes Syndrome (SIDDT) by a SNP Genome Scan and Identification of TSPYL Loss of Function*, 101 Proceedings of the National Academy of Sciences 11689 (2004). The similar project on the neurological disease is described in Kevin A. Strauss et al., *Genome-Wide SNP Arrays as a Diagnostic Tool: Clinical Description, Genetic Mapping, and Molecular Characterization of Salla Disease in an Old Order Mennonite Population*, 138A American Journal of Medical Genetics 262 (2005); *see also* Lisa Belkin, *A Doctor for the Future*, N.Y. Times Magazine, Nov. 6, 2005, at 68.

[9] For just this reason, ten pharmaceutical firms, together with the Wellcome Trust, created a consortium to obtain rights to a large number of such SNPs and to keep the use of these SNPs in the public domain. Ehsan Masood, *Consortium Plans Free SNP Map of Human Genome*, 398 Nature 545 (1999); *The SNP Consortium*, http://snp.cshl.org/ (last visited Dec. 21, 2005). The pharmaceutical industry would not have had to undertake this expensive program had it been clear that SNPs, as natural phenomena, would not have been patentable.

[10] An example is the U.S. National Human Genome Research Institute's Research Roadmap. *See* Francis S. Collins et al., *A Vision For The*

Current research focuses on regulatory controls for the genetic code emphasizing that:

> Genes and gene products do not function independently, but participate in complex interconnected pathways, networks and molecular systems that, taken together, give rise to the workings of cells, tissues, organs, and organisms.[11]

As a recent study by the National Research Council of the National Academy of Sciences noted, "Today systems biologists study the complex interplay of a host of genes as these genes give rise to a disease symptom, such as hypertension, or analyze hundreds of proteins in a blood sample to identify patterns that may be indicative of a particular cancer."[12] Thus "[t]he pattern of a single investigator working on a single gene or gene sequence is giving way to more multi-investigator projects entailing work on many genes or proteins simultaneously, more and more of them patented."[13]

Patents that claim the underlying natural phenomena and biochemical relationships will greatly impede this new and more complex genomic research. Unfortunately, this is not a hypothetical example. It has already occurred in at least one case—that of the heavily criticized BRCA patents, U.S. Patents 5,693,473, 5,709,999, and 5,747,282. These patents describe mutations that contribute to susceptibility to breast cancer, and include claims that reach any method of detecting

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Future Of Genomics Research: A Blueprint For The Genomic Era, 422 Nature 1 (2003).

[11] *Id.* at 4.

[12] National Research Council Committee on Intellectual Property Rights in Genomic and Protein Research and Innovation, REAPING THE BENEFITS OF GENOMIC AND PROTEOMIC RESEARCH: INTELLECTUAL PROPERTY RIGHTS, INNOVATION, AND PUBLIC HEALTH 35 (forthcoming 2006) (*available at* www.nap.edu/books/0309100674/html/).

[13] *Id.* at 106.

these mutations. Like claim 13 of patent '658, the operative claims in these patents are on a fact of nature. The U.S. holder of these patents has exercised its exclusivity by prohibiting others from providing the tests,[14] making it impossible for a patient to obtain a second opinion on the result,[15] and preventing other laboratories from effectively building a data base of other mutations affecting breast cancer. As the National Research Council states:

> the exclusive practice of any medical procedure or clinical diagnostic test is an important issue for the medical profession and raises important questions of public health and science policy. For example, the performance of a gene-based clinical test in an academic setting often generates rich databases of newly detected genetic variations that can be correlated with an array of clinical phenotypes. Such admixed medical practice and research provides important new information about the mutational repertory of specific disease-linked genes, as well as the phenotypic correlations that provide new insights into disease mechanisms and identify potential new targets for therapeutic intervention.[16]

For these reasons, there are special dangers in allowing only one laboratory exclusive rights to conduct research on a particular genetic phenomenon, such as the relation between homocysteine and cobalamin or folate, as upholding claim 13 would entail. Science will advance more rapidly, with benefits to patients, if laboratories may both compete with and

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[14] *Id.* at 19.

[15] *Id.* at 111.

[16] *Id.* at 125. In this case, patents may already have harmed medicine. There are reports that the exclusive supplier of the tests has missed relevant mutations. *See* Jordan Paradise, *European Opposition to Exclusive Control Over Predictive Breast Cancer Testing and the Inherent Implications for U.S. Patent Law and Public Policy: a Case Study of the Myriad Genetics' BRCA Patent Controversy*, 59 Food & Drug L.J. 133, 147 (2004).

collaborate with one another through common access to laws of nature.

C. Invalidating Claim 13 Would Neither Eliminate Incentives To Invest In Research Nor Disrupt The Patent System

The state of the law with respect to ownership of genetic relationships is relatively unsettled. This has resulted in a well-documented "land-grab" mentality, in which patent attorneys seek gene patents at the outer boundaries of the line between human invention and phenomena of nature.[17] This is not surprising, for without guidance about the scope of valid versus invalid subject matter, patent attorneys are obliged seek the broadest possible claims for their clients. *See Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1382 (Fed. Cir. 2000) (a patent attorney has a "professional responsibility . . . to assist his or her client in defining her invention to obtain, if possible, a valid patent with maximum coverage").

Just because these pressures have led patent attorneys to seek and sometimes obtain patents that stretch the boundaries of patentability into the natural realm, however, does not mean that such increased scope is necessary to advances in science. This case presents a vital opportunity for this Court to curb this pressure on the outer boundaries of patentability, and to return the balance to the baseline set by this Court in *Diehr* and related decisions.[18] In so doing, there is little dan-

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[17] *See* Jensen & Murray, *supra* note 7.

[18] Some guidance in this area might well be provided by developments in areas of patent law other than the scope of patentable subject matter. For example, a recent Federal Circuit decision struck down the validity of patent claims directed to short fragments of DNA sequences (called "Expressed Sequence Tags" or "ESTs") without a known function as lacking specific and substantial utility as required by the patent laws. *In re Fisher*, 421 F.3d 1365 (Fed. Cir. 2005). But such approaches cannot be as systematic and useful as curtailing the "land grab" in patentable subject matter.

ger that genetic or other biomedical research will be harmed by reduced incentives for making discoveries.

This is so for two reasons. *First,* nothing in the argument advanced by *Amici* here would impede patents in the genetic area if those patents involved more than the mere observation and recitation of a law of nature. Consistent with this Court's test in *Diehr, Amici* do not oppose patent claims directed to applications of laws of nature. Thus the scope of patentable subject matter still may legitimately extend to innovative tests, or inventive pharmaceutical compositions, or new and useful therapies, or any number of inventions in technology that researchers have yet to imagine, that add human invention to a natural phenomenon. The issue here is whether ownership rights should be able to result from the mere *discovery* of a natural phenomenon.

For example, the BRCA example described above involved patent claims on a gene that provides susceptibility to breast cancer. The gene at issue is a stretch of DNA with a particular sequence that codes for a particular polypeptide called BRCA1. The 5,747,282 patent asserts ownership over DNA that codes for this polypeptide; claim 1 of that patent reads: "1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2."

Like claim 13 of the '658 patent involved in this case, the BCRA patent seeks to claim exclusive rights to an underlying natural relationship. Anyone with this gene has this sequence in her DNA. Like amino acids and vitamins, both DNA and the polypeptide exist naturally in the body, as does the relationship between them. In both cases, the researchers made a discovery, not an invention. Owning such a stretch of DNA thus prevents others from working with that DNA even though it occurs naturally. Simply finding the DNA, however, can readily be distinguished from inventive methods used to find the DNA, or inventive therapies and tests using the DNA.

The latter would be legitimately patentable under the principles set forth in *Diehr*, and ownership of rights to such tests and therapies is adequate to ensure research into isolating the gene sequence in the first place.

Second, ruling *claims* like claim 13 invalid will not necessarily invalidate any *patents per se*. Claims define the metes and bounds of what the patent holders consider their exclusive rights. Each claim defines the scope of a different invention. 35 U.S.C. § 112. Patents contain multiple claims because patent applicants are allowed to claim several inventions based upon a single technical disclosure. Indeed, standard patent practice is to file a number of claims of varying scope precisely to protect against future uncertainty. Broad claims have the greatest coverage, but the highest likelihood of being invalidated (*e.g.*. by prior art). Narrow claims have the best chance of avoiding prior art, but offer the least coverage. Thus, one does not infringe a patent; one infringes a patent claim. Likewise, a court does not determine that a patent is invalid; it determines whether some or all of the claims are invalid.

The inventors of the patent at issue in this suit filed thirty-four claims based upon their work, only one of which (claim 13) is challenged. Invalidating claim 13 does not invalidate the entire patent. It simply removes the single, unpatentable claim. It is significant that there is no challenge here to the patentable subject matter of many of the '658 patent's thirty-three other claims, and that Petitioner pays royalties for its use of those inventions. Many of the '658 patent's claims are directed to specific testing methods and detailed test protocols, not to the underlying natural phenomenon itself, as is claim 13. These claims will continue to be valid and enforceable even if the outlier claim 13 is struck down.

Thus a decision for Petitioner in this case might call into question certain claims in certain patents, including in the area of gene patents, but need not invalidate all those patents

themselves. The claims that are invalidated will be those that are on the outer edge of patentability and reflect not justifiable reliance on the state of the law, but zealous patent attorneys seeking the broadest possible scope for their clients.

If the Court had any lingering concern that invalidation of claim 13 would upset the settled expectation of those who might have already obtained patents issued under an incorrect interpretation of *Diehr*, then the Court might issue a prospective ruling affecting only patents issued in the future. This approach is not necessary, however, for it is appropriate and expected that judicial rulings upon the scope of patentable subject matter might affect the future application of claims in patents that have already issued. For instance, this Court recently provided guidance on the scope of the doctrine of equivalents. *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002). This doctrine allows for infringement liability even if there is no literal infringement of the claim. Although this decision certainly altered previous expectations about the scope of patent enforceability, it has been applied by the lower courts to all issued patents. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 344 F.3d 1359, 1370 n.4 (Fed. Cir. 2003) (*en banc*) (on remand) (citing *Harper v. Va. Dep't of Taxation*, 509 U.S. 86, 97 (1993) ("When this Court applies a rule of federal law to the parties before it, that rule is the controlling interpretation of federal law and must be given full retroactive effect in all cases still open on direct review and as to all events, regardless of whether such events predate or postdate our announcement of the rule.")).

D. If There Is Any Ambiguity About The Patentability Of Natural Phenomena, It Should Be Resolved In Favor Of Petitioner In Order To Avoid Serious Constitutional Questions

Just as this Court interpreted copyright law so as to ensure consistency with the Constitution, *Feist Publ'ns, Inc. v. Rural*

Tel. Serv. Co., 499 U.S. 340 (1991), so too should it interpret patent law. There are two constitutional problems with the patent claim at issue in this case, and with all patents claiming exclusive rights to the results of a measurement of nature.

The first problem is that patents on measurements of nature, like the copyright struck down in *Feist*, deal with facts themselves. The corresponding lack of originality raises serious questions under Art. I, § 8, which gives Congress authority to issue patents that "promote the *Progress* of Science and useful Arts." Art. I, § 8, cl. 8 (emphasis added). Patents on measurements of nature take information *out* of the public domain rather than putting ideas *into* the public domain as is the intention of the Constitution and of the patent disclosure provisions, 35 U.S.C. § 112. In the present case, for example, a scientist or doctor was free before the patent issued to use a total homocysteine test and make whatever guess he or she might wish about cobalamin or folate deficiency. It was infringement to do so, however, after the patent issued. The subject matter provision of the Patent Act, 35 U.S.C. § 101, therefore should be interpreted to prohibit patents that preempt the use of principles or measurements of nature and that, in effect, bar future researchers from making such measurements or from using information that is available from nature. Otherwise, the patent does not "promote the Progress of Science."[19]

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[19] Nor is this constitutional difficulty resolved by the fact that the Patent Clause gives Congress authority to grant patents to "inventors" for their "discoveries." Contrary to the modern usage of "discovery," the term had a different meaning in the eighteenth century, when the Constitution was ratified. "A discovery in that era, as used in the intellectual property law, denoted something originating from the human intellect and not merely learned by that intellect." Linda J. Demaine & Aaron Xavier Fellmeth, *Reinventing the Double-Helix: A Novel and Nonobvious Reconceptualization of the Biotechnology Patent*, 55 Stan. L. Rev. 303, 370 (2002); *see also* H.R. Rep. No. 71-1129, at 16-17 (1930); Albert H. Walker, TEXT-BOOK OF THE PATENT LAWS OF THE UNITED STATES OF

A second constitutional difficulty with patent claims on measurements of nature is that the patent might have a significant chilling effect on publication in violation of principles of freedom of speech protected by the First Amendment. Under normal patent law principles, if claim 13 is valid, a scientist, doctor, or medical firm publishing an article encouraging the use of a total homocysteine measurement as a way of inferring cobalamin or folate deficiency might be found to have induced infringement under 35 U.S.C. § 271(b) ("Whoever actively induces infringement of a patent shall be liable as an infringer."). For a scientist publishing without knowledge of the patent, such liability depends on the relevant standard for the intent requirements needed to trigger liability as a inducing infringer. It is uncertain whether these standards require specific intent, *see Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544 (Fed. Cir. 1990), or only intent to cause the acts which constitute infringement, *see Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464 (Fed. Cir. 1990). *See generally* Mark A. Lemley, *Inducing Patent Infringement*, 39 U.C. Davis L. Rev. 225 (2005).

No scientist should need to undertake an analysis of the intent requirements for inducing infringement before publishing a research article on a direct correlation between a measurement and a natural phenomenon. No one can make such a measurement with the relevant purpose and not infringe a patent claim such as claim 13. Nor can anyone publish an

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AMERICA § 2, at 2-3 (2d ed. 1889) ("The word 'discovery' does not have, either in the Constitution or the statute, its broadest signification. It means invention, in those documents, and in them it means nothing else."). Case law from the early days of patent jurisprudence reflects this understanding. *In re Kemper*, 14 F. Cas. 286, 287 (C.C.D.C. 1841) (Discovery as used in the Constitution is "synonymous with invention. . . . The applicant must invent, contrive, or produce something that did not exist before."). Thus one cannot "discover" a law of nature any more than one can "invent" a law of nature, as those terms were used within the original meaning of Art. I, § 8, cl. 8.

article about the correlation or include discussion of the correlation in a scientific or medical treatise without risking contributory infringement. A spread of such patents would have an enormous chilling effect on scientific and commercial publication.

These constitutional considerations should provide an additional reason to reaffirm the *Diehr* principle by ruling for Petitioners in this case.

CONCLUSION

For the reasons stated above, the decision below should be reversed or vacated.

Respectfully submitted,

BARBARA A. CAULFIELD
AFFYMETRIX, INC.
3380 Central Expressway
Santa Clara, CA 95051
(408) 731-5151

KATHLEEN M. SULLIVAN
Counsel of Record
BRIAN C. CANNON
QUINN EMANUEL URQUHART
OLIVER & HEDGES, LLP
555 Twin Dolphin Drive,
Suite 560
Redwood Shores, CA 94065
(650) 801-5000

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LABORATORY CORPORATION OF AMERICA HOLDINGS (doing business as LabCorp),

Petitioner,

v.

METABOLITE LABORATORIES, INC. and COMPETITIVE TECHNOLOGIES, INC.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

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BRIEF OF THE AMERICAN CLINICAL LABORATORY ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

ROY T. ENGLERT, JR.*
DANIEL WALFISH
Robbins, Russell, Englert, Orseck & Untereiner LLP
1801 K Street, N.W.
Suite 411
Washington, D.C. 20006
(202) 775-4500

* *Counsel of Record*

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BRIEF OF THE AMERICAN CLINICAL LABORATORY ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

INTEREST OF THE *AMICUS CURIAE*[1]

The American Clinical Laboratory Association ("ACLA"), a not-for-profit industry association, is the nation's leading organization representing clinical laboratories. ACLA's twenty-four members include local, regional, and national laboratories, and they furnish testing services to patients in all 50 States and the District of Columbia. ACLA estimates that its members supply roughly 60% of all clinical laboratory testing nationwide that is not provided by laboratories affiliated with hospitals or physicians' offices. Founded in 1971, ACLA regularly advocates the interests of its members before the federal and state legislatures and administrative agencies, as well as in dealings with other health care organizations and the public. ACLA previously appeared as an *amicus curiae* in another case before this Court, *Vermont Agency of Natural Resources* v. *United States ex rel. Stevens*, 529 U.S. 765 (2000).

ACLA's mission includes encouraging the highest standards of quality, service, and ethical conduct among its members. Each member company pledges to promote public health and patient welfare by providing the highest quality testing services.

ACLA and its members have a strong interest in the proper resolution of this case. Respondents in effect claim ownership over a natural biochemical relationship. If they prevail, any researcher who discovers a chemical association in the human body will be able to claim a monopoly over any future

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[1] All parties have consented to the filing of this brief. The parties' letters of consent have been lodged with the Clerk of the Court. Pursuant to Rule 37.6, *amicus curiae* states that no counsel for a party has written this brief in whole or in part and that no person or entity, other than the *amicus curiae*, its members, or its counsel, has made a monetary contribution to the preparation or submission of this brief.

diagnostic test based on that association. Petitioner here began using a novel testing technique (the Abbott Laboratories assay) that is not covered by the disputed patent but that measures some of the same substances as the respondents' patented assays. This is not at all unusual. Independent laboratories frequently introduce new tests and improvements on existing tests. These innovations are sometimes developed in house at the independent laboratory company and sometimes developed by outside entities. No matter where they are developed, such innovations typically derive their clinical significance from previously known natural biological relationships.

Under the view of patentability taken in the decision below, these innovations either would not be brought to market at all or would become available only at higher prices and on a limited basis. Either way, laboratories' ability to provide new life-saving tests and patients' access to those tests would suffer. The result would be not just economic harm but also interference with ACLA's and its member laboratories' goal of providing the highest level of testing services.

SUMMARY OF ARGUMENT

Claim 13 of respondents' patent is extraordinary. It recites a "method" for detecting a deficiency of one of two vitamins that consists in its entirety of the following two steps: (1) assay body fluid for elevated levels of the amino acid homocysteine and related molecules, and (2) "correlate" elevated levels of those substances with the existence of a deficiency of one of the vitamins. To infringe claim 13, it is *not* necessary to use respondents' patented methods for performing the assaying step. Thus, the only real content to claim 13 is the scientific insight that deficiencies of certain vitamins are associated with elevated levels of homocysteine. This statistical relationship between chemicals in the human body, however, is a phenomenon of nature and therefore unpatentable.

A ruling for respondents would radically alter the patent regime in this country to the great detriment of clinical labora-

tory testing services. Nearly every clinical laboratory test involves an "assay" followed by the application of some kind of natural correlation. New tests and improvements on existing tests are being developed and introduced all the time. Invariably these innovations – many of which quite properly receive patent protection – build on and derive their significance from previously established biological relationships.

To hold claim 13 valid, however, is to say that the discoverers of those relationships can patent the relationships themselves and thereby gain the right to prevent doctors from using the results of any laboratory assays, even ones not covered by the patent. For example, the researchers who discovered the correlation between risk of coronary heart disease and levels of "bad" cholesterol could have gained the right to prevent doctors from using the results of any "bad" cholesterol measurement to assess risk of heart disease, and the researchers who discovered the correlation between the presence of prostate cancer and levels of prostate-specific antigen, or PSA, could have gained the right to prevent doctors from using the results of any PSA assay to screen for or monitor prostate cancer. That is not, and never has been, the law.

Claim 13 is not saved by following this Court's instructions in *Diamond* v. *Diehr*, 450 U.S. 175 (1981), to examine the method "as a whole." The only information in the claim other than the unpatentable natural relationship is an unspecified "assay" step. But the recital of this step is insignificant in context. To apply a natural correlation between two variables, one must somehow measure one of the variables. Of course, a particular method of measurement might well be the subject of a valid patent. A perfect example is the very patent at issue in this case, which describes novel homocysteine assay techniques in a set of claims that are conceded to be valid. Claim 13, by contrast, does not indicate how to perform the assay before plugging its results into the correlation; it merely directs that some kind of assay is needed. That is profoundly inadequate.

Claim 13 fails as well because it would extend, in violation of patent law and general principles of intellectual property protection, to every practical application of the natural principle it describes. Moreover, contrary to the suggestion of the United States in its earlier brief, the fact that the assay step of the "process" might entail the physical or chemical alteration of a sample of fluid is irrelevant to the claim's validity. The alleged infringement in this case is *doctors'* "correlation" of the assay results with vitamin deficiencies, not the clinical laboratories' performance of the assaying. Petitioner has been held liable for induced, not direct, infringement. Finally, unnecessarily broad language from several Federal Circuit decisions in conflict with this Court's precedents does not support the validity of claim 13.

ARGUMENT

I. The Disputed Patent Claim Is Invalid Because It Seeks To Protect Nothing More Than A Naturally Occurring Biochemical Relationship – A Quintessentially Unpatentable Discovery

This Court has said repeatedly, since at least as far back as the mid-19th century, that "a scientific truth * * * is not patentable invention," *Mackay Radio & Tel. Co.* v. *Radio Corp. of Am.*, 306 U.S. 86, 94 (1939). "Phenomena of nature, though just discovered * * * are not patentable, as they are the basic tools of scientific and technological work." *Gottschalk* v. *Benson*, 409 U.S. 63, 67 (1972); accord *Diamond* v. *Diehr*, 450 U.S. 175, 185 (1981); *Diamond* v. *Chakrabarty*, 447 U.S. 303, 309 (1980); *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948); *O'Reilly* v. *Morse*, 56 U.S. (15 How.) 62, 116 (1853). A patent claim that recites only scientific truth or natural phenomena is invalid because it does not describe a "process" or any other subject matter patentable under 35 U.S.C. § 101.

It is a matter of basic scientific knowledge that two B vitamins – cobalamin (also known as B_{12}) and folate (also known as

folic acid) – are necessary to break down the amino acid known as homocysteine in the human body's normal metabolic processes. If one of those vitamins is lacking, the body will not properly process homocysteine, and the level of homocysteine will therefore be elevated. The researchers who filed the '658 patent discovered that an abnormally high level of "total homocysteine" – meaning the combination of homocysteine and several related molecules – is a reliable signal of abnormally low levels of at least one of those B vitamins. Or, as the patent puts it: "It has now been discovered that an elevated level of total homocysteine in tissues of warmblooded animals correlates both with cobalamin deficiency and with folic acid deficiency." S.A. 11, col. 4, ll. 17-20.

This knowledge falls squarely in the category of unpatentable natural phenomena. The quantitative relationships between the levels of total homocysteine and the B vitamins are simply observable consequences of certain chemical processes that take place constantly in every cell in the human body. Like the qualities of certain bacteria that were found not to inhibit each other's ability to fix nitrogen in certain plants, see *Funk Bros.*, 333 U.S. at 130, the statistical associations in question here are "manifestations of laws of nature, free to all men and reserved exclusively to none," *ibid.*

There is no content to claim 13 beyond these natural biological relationships. Claim 13 sets forth two steps: (1) assay for – in other words, measure the amounts of – homocysteine, and (2) "correlate" the amounts of homocysteine with the existence of a deficiency in cobalamin or folate.

"Correlate" for present purposes has a meaning different from the word's usual one in research and clinical laboratory science. Normally "correlate" means "to establish a mutual or reciprocal relation" between variables, "to determine, establish, or show a usu. causal relationship between," "to put in relation with each other," "present or set forth so as to show relationship," etc. WEBSTER'S THIRD NEW INTERNATIONAL DICTIONARY 511 (1986). For example, a researcher who discovers

that elevated levels of cholesterol are statistically associated with increased risk of heart disease has *correlated* cholesterol levels with risk of heart disease. Once that relationship is known, a physician who observes elevated cholesterol in a patient and infers that the patient has an increased risk of heart disease has not correlated the two variables at all but rather *applied* the correlation.

In this case, the relationship between levels of homocysteine and the B vitamins was established through research performed by the inventors of the '658 patent and others. The alleged infringement on the part of doctors is not correlating in its usual sense, because the doctors are not *establishing* the relationship between homocysteine and the B vitamins (each physician is not, for example, performing separate controlled experiments on large numbers of patients) but rather *applying* that relationship in specific instances as part of patient care.

The Federal Circuit interpreted "correlating" in claim 13 to mean "*relating* total homocysteine levels to cobalamin or folate deficiency," Pet. App. 12a (emphasis added) – that is, *applying* in a specific instance the previously established general relationship.[2] Thus correlating for present purposes means only conducting the intellectual exercise of applying the previously established relationship between elevated homocysteine and vitamin B deficiencies to a specific patient's homocysteine levels.

The first step of claim 13 – "assay" – can be performed by any means, whether patented or unpatented. Obviously the use of an assay not specified in the '658 patent cannot be an in-

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[2] The district court effectively interpreted "correlating" in the same way. Although the district court stated that it construed the term to mean "to establish a mutual or reciprocal relationship between," JA 60-61, it, like the Federal Circuit, obviously understood claim 13 to be drawn to the everyday business of applying a relationship rather than the far rarer undertaking of establishing one. See *ibid.* (holding that the term "describes a discrete step in a sequential process").

fringement of that patent, and respondents have never claimed that petitioner committed acts of infringement when it used the Abbott assay.[3] Moreover, homocysteine levels are routinely measured to screen for conditions entirely distinct from vitamin deficiency – in particular, risk of heart attack or stroke. See, *e.g.*, American Association for Clinical Chemistry, "Homocysteine," *in* Lab Tests Online, http://labtestsonline.org/understanding/analytes/homocysteine/glance.html; see also David S. Wald et al., *Homocysteine and Cardiovascular Disease: Evidence on Causality from a Meta-Analysis*, 325 BMJ 1202 (2002) (noting association between elevated homocysteine levels and cardiovascular disease). The patent is not addressed to the correlations between homocysteine and heart disease or stroke. Accordingly, merely assaying for homocysteine or total homocysteine cannot possibly infringe the patent. Thus infringement of claim 13 must occur with the performance of the second step – the "correlating" or "relating." See also Pet. App. 13a ("[T]he parties hinge the direct infringement issue solely on whether the physicians perform the correlating step.").

The relating step, however, as the Federal Circuit explained, "is a simple conclusion that a cobalamin/folate deficiency exists *vel non* based on the assaying step." Pet. App. 18a. That is, this step consists of nothing more than applying (unpatentable) fundamental scientific knowledge to the results of an (unspecified) assay. To claim, as respondents have, an exclusive right to engage in that analysis is to arrogate impermissibly the biological relationship between homocysteine and the B vitamins.

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[3] Unlicensed performance of *respondents'* patented assaying methods would be an act of infringement, but only of claims in the '658 patent other than claim 13, and in any event petitioner has paid respondents for every assay it has conducted using their methods.

II. A Holding That Claim 13 Is Patentable Would Cripple Progress In Clinical Laboratory Testing

If respondents succeed in their effort to monopolize the natural statistical relationship between an elevated level of total homocysteine and the existence of a B vitamin deficiency, the harm to clinical laboratory services in this country will be immeasurable. Anyone who discovers any natural correlation in the human body with potential diagnostic significance will be able to block laboratories and physicians from administering tests based on that correlation, even when the tests did not exist at the time the correlation was discovered.

That is precisely what happened in this case. The Abbott total homocysteine assay did not exist at the time the '658 patent was issued. No one suggests that that assay standing alone infringes the '658 patent – just as no one disputes the validity of the claims in the '658 patent directed to the inventors' methods of assaying for total homocysteine. On the contrary, respondents contend that doctors infringed claim 13 of the '658 patent when they analyzed the results of the (non-infringing) Abbott assay. That is, respondents seek to prevent physicians from using any homocysteine assay at all in the diagnosis of the vitamin deficiencies where license agreements are lacking. Accepting respondents' position would pervert the purposes of patent law by stifling innovation rather than encouraging it.

The standard system for coding medical services – Current Procedural Terminology, or CPT, see AMERICAN MEDICAL ASSOCIATION, CURRENT PROCEDURAL TERMINOLOGY (2005) (hereinafter CPT 2006) – contains approximately 1100 codes for clinical laboratory tests. See CMS, 2006 CLINICAL DIAGNOSTIC LABORATORY FEE SCHEDULE (Nov. 16, 2005), available at http://www.cms.hhs.gov/ClinicalLabFeeSched/02_clinlab.asp. Each code corresponds to anywhere from one to dozens of commercially available assays. Nearly all of these at some level – and often at a level of far greater technical and diagnostic sophistication than the "method" in claim 13 – are based on a

"correlation" of some kind. After all, in every case, something must be tested, and the results of that test must be translated into clinically meaningful terms through the application of scientific knowledge about the relationships between variables.

Tests, moreover, are constantly being introduced and improved. See, *e.g.*, Kristian Linnet & James C. Boyd, *Selection and Analytical Evaluation of Methods – With Statistical Techniques*, *in* TIETZ TEXTBOOK OF CLINICAL CHEMISTRY AND MOLECULAR DIAGNOSTICS 353, 353 (Carl A. Burtis et al., eds., 4th ed. 2006) (hereinafter TIETZ TEXTBOOK). The 2006 set of CPT codes includes 29 new ones for laboratory procedures; the number was 19 for 2005. See CPT 2006, at 433; AMERICAN MEDICAL ASSOCIATION, CURRENT PROCEDURAL TERMINOLOGY 408 (2004). The number of new tests actually introduced each year is far greater because codes can correspond to multiple tests. In every instance, the new and improved products are inventive applications of previously discovered laws of nature. And, of course, those innovations are frequently the subjects of patents.

But, if the decision below is affirmed, the availability of new and improved tests would be entirely at the mercy of the person who first discovered the natural correlation that makes the test useful. Progress in clinical laboratory testing in this country never has been, and never should be, subject to such constraints. Several examples should illustrate just how extraordinary it really would be to hold that claim 13 states a patentable process.

Increased risk of coronary heart disease has been correlated with, among other things, elevated levels in the blood of LDL (low-density lipoprotein) cholesterol, also known as "bad" cholesterol. See, *e.g.*, Nader Rifai & G. Russell Warnick, *Lipids, Lipoproteins, Apolipoproteins, and Other Cardiovascular Risk Factors*, *in* TIETZ TEXTBOOK 903, 938. When doctors first began to focus on levels of LDL cholesterol, technology for measuring it directly was not widely available for clinical use. Instead, LDL levels were *estimated indirectly*

using a calculation based on the levels of (a) total cholesterol and (b) other categories of cholesterol besides LDL, all of which could be measured directly. See *id.* at 938, 948.

Today a variety of assays for directly measuring levels of "bad" cholesterol are commercially available. Some of these are "enzyme immunoassays," meaning that they use chemical reactions with substances that react specifically with LDL. Others involve isolating LDL cholesterol using chemicals that either selectively dissolve away the other cholesterol molecules but not LDL, or dissolve away LDL but not the other cholesterol molecules. Rifai & Warnick, *supra*, at 951. All have certain advantages over the indirect method: they can be readily automated, they avoid the distorted estimates that sometimes result from the indirect calculations, and a number of them appear to yield accurate results even when the patient does not fast before the blood is drawn. See *id.* at 942, 949, 952.

It follows from respondents' position that the researchers who established the correlation between elevated levels of LDL cholesterol and risk of coronary heart disease could have gained patent protection for a "method for detecting an increased risk of coronary heart disease comprising the steps of: (1) assaying a blood sample for an elevated level of LDL cholesterol; and (2) correlating an elevated level of LDL cholesterol in said blood sample with an increased risk of coronary heart disease." If that had happened, every time a doctor assessed risk of coronary heart disease using the results of an LDL cholesterol test[4] – including the newer assays that directly measure LDL cholesterol – the doctor would be committing patent infringement. This scenario is absurd, but the hypothetical facts are analytically indistinguishable from the present case. And this

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[4] Congress has specifically directed the Medicare program to pay for cholesterol and other lipid testing – a category that includes measurement of LDL levels – "for the early detection of cardiovascular disease (or abnormalities associated with an elevated risk of cardiovascular disease)." 42 U.S.C. § 1395x(xx)(1); *id.* § 1395x(s)(X).

analysis could be repeated for practically every test conducted by a clinical laboratory in this country.

To take another example, in the late 1980s and early 1990s, it became known that the presence of prostate cancer correlates with an elevated level in body fluids of a protein known as prostate-specific antigen, or PSA. See, *e.g.*, William J. Catalona et al., *Measurement of Prostate-Specific Antigen in Serum as a Screening Test for Prostate Cancer*, 324 N. ENG. J. MED. 1156 (1991). The seminal study, published in 1987, used an assay known as a "double-antibody radioimmunoassay" that was developed by one of the researchers. See Thomas A. Stamey et al., *Prostate-Specific Antigen as a Serum Marker for Adenocarcinoma of the Prostate*, 317 N. ENG. J. MED. 909 (1987). This study demonstrated that PSA could be used to track the progress of prostate cancer in patients already known to have it. *Ibid.*

PSA testing is now a standard screen for prostate cancer. See, *e.g.*, Ian M. Thompson et al., *Prevalence of Prostate Cancer Among Men with a Prostate-Specific Antigen Level ≤ 4.0 ng per Milliliter*, 350 N. ENG. J. MED. 2239 (2004); Michael J. Barry, *Prostate-Specific-Antigen Testing for Early Diagnosis of Prostate Cancer*, 344 N. ENG. J. MED. 1373 (2001). In fact, Congress has specifically required Medicare to cover, for all male Medicare beneficiaries over the age of 50, annual PSA testing (among other tests) "for the purpose of early detection of prostate cancer," 42 U.S.C. § 1395x(oo); *id.* § 1395x(s)(P).

Since the late 1980s, a wide variety of PSA assays have become commercially available. See, *e.g.*, Alexander Haese et al., *Clinical Evaluation of the Elecsys Total Prostate-Specific Antigen Assay on the Elecsys 1010 and 2010 Systems*, 48 CLINICAL CHEMISTRY 944 (2002); Robert L. Vessella et al., *Evaluation of the Abbott IMx® Automated Immunoassay of Prostate-Specific Antigen*, 38 CLINICAL CHEMISTRY 2044 (1992); Sunjay Jain et al., *Improving the Utility of Prostate Specific Antigen (PSA) in the Diagnosis of Prostate Cancer*, 78 POSTGRAD MED. J. 646 (2002); D. Patel et al., *A Comparison of*

Six Commercial Assays for Total and Free Prostate Specific Antigen (PSA), 85 BJU INT'L 686 (2000). Most of these assays are not radioimmunoassays, but other kinds of assays – enzyme immunoassays, "fluoroimmunoassays," and "chemiluminescence immunoassays." See Daniel W. Chan et al., *Tumor Markers*, *in* TIETZ TEXTBOOK 745, 760. The different types of assays are based on somewhat different chemical principles, and each assay uses different materials and equipment. See generally L.J. Kricka, *Principles of Immunochemical Techniques*, *in* TIETZ TEXTBOOK 219, 234-239.

Each assay typically has comparative advantages and disadvantages, including differences in sensitivity and ability to discriminate between different conditions. See Patel, *supra*, 85 BJU INT'L at 688-689. Most have the advantage over radioimmunoassays that they do not use radioactivity and thereby avoid the handling, storage, and disposal difficulties associated with it. Amid the development of all of these tests, however, the basic scientific principle that makes a PSA assay clinically useful – namely, the natural association between elevated PSA levels and prostate cancer – has been the same.

If claim 13 is upheld, the researchers who demonstrated (using a unique assay they had developed) the association between PSA levels and the progress of prostate cancer could have gained a valid patent claiming a "method" for tracking the progress of prostate cancer by (1) assaying a body fluid for the level of PSA; and (2) correlating the level of PSA with the stage of prostate cancer. The owners of that patent would have been able to claim infringement every time doctors use a PSA assay – *any* PSA assay, including all of the immunoassays developed after the hypothetical patent was issued – to monitor the course of prostate cancer or even to screen for it. Such a regime would have severely impeded advances in prostate cancer treatment and screening, if not foreclosed them entirely.

Because those responsible for advances in the diagnosis of risk of coronary heart disease using cholesterol measurements, and in the diagnosis of prostate cancer using PSA measure-

ments, did not attempt to patent claims as broad as claim 13 in the '658 patent, medical science has been able to advance to its current state without the payment of royalties and consequent discouragement of research that such patent claims would have brought about. A decision by this Court upholding claim 13, however, would permit those who make medical advances in the future to patent every potential application of the natural phenomena that underlie their inventions.

Our law does not permit, and never has permitted, such a result. Until now, the patent laws have facilitated innovation in medicine and laboratory science by conferring protection on novel applications of biological phenomena while leaving the phenomena themselves free for other inventors to use. Claim 13, however, arrogates the phenomenon itself. A ruling upholding it would be a major shift in our patent regime, one that would do incalculable damage to the business of ACLA's members and – more important – to the ability and incentives of researchers to make advances in the state of the art of medical diagnosis using laboratory tests.

III. This Court's Precedents Foreclose Any Argument That Claim 13 Discloses A Patentable Process Rather Than An Unpatentable Principle

A. Respondents cannot prevail by arguing that the validity of claim 13 should be determined with reference to the method "as a whole," *Diehr*, 450 U.S. at 188, as opposed to the patentability of individual steps in isolation. There is if anything less to this patent claim than meets the eye.

Viewed in its entirety, claim 13 recites nothing other than that one can ascertain the existence of a cobalamin or folate deficiency by measuring levels of homocysteine. That information, if not a mere reformulation of the natural relationships between levels of homocysteine and the vitamins, at most is a blindingly obvious corollary to those relationships. If it is known that elevated amounts of substance A signify diminished amounts of substance B or C, it follows automatically that one

can determine whether there are diminished amounts of substance B or C by measuring the levels of substance A.

A claim that recites only an unpatentable natural relationship and an additional insignificant step is not a "process" for purposes of 35 U.S.C. § 101. In *Diehr*, this Court squarely stated: "insignificant post-solution activity will not transform an unpatentable principle into a patentable process." 450 U.S. at 191-192. In this case there is no post-solution activity at all, let alone significant post-solution activity. There is an instruction regarding pre-solution activity – namely, "conduct some kind of assay" – but it is "insignificant" within the meaning of *Diehr*. Obviously, to apply the (unpatentable) knowledge that elevated total homocysteine correlates to vitamin deficiencies, one must first somehow measure the amounts of total homocysteine.

This is not to say that an assay itself is an insignificant invention. On the contrary, assay techniques frequently are the product of great ingenuity, and innumerable assays are protected by valid patents. Indeed, this case includes a perfect example. Claims 1 through 12 of the '658 patent are directed to the inventors' novel methods for determining total homocysteine levels. Those methods involve mixing specified substances together, taking readings on a mass spectrometer, and applying specified calculations to those results. By contrast, the "assay" step recited in claim 13 says nothing about how to perform the measurement. It simply says that, somehow, a measurement must be performed.

The *Diehr* patent was upheld even though the claimed process for curing rubber made use of a mathematical formula known as the Arrhenius equation. That is because the inventors did not seek to patent the equation itself, a basic law of chemistry that predicts the rate of a chemical reaction as a function of temperature, see, *e.g.*, NEIL JESPERSEN, GENERAL CHEMISTRY 453-455 (1997), and that had "long been used to calculate the cure time in rubber-molding" processes, 450 U.S. at 177 n.2. Rather, the inventors sought to protect only "the use of that equation in conjunction with all of the other steps in their

claimed process." *Id.* at 187. What made the *Diehr* invention innovative was the continuous measuring of temperature inside the rubber-curing mold, which permitted a computer programmed with the Arrhenius equation to update the cure time continuously, which in turn allowed the computer to open the mold at the right time automatically and thereby achieve a more precise curing time than would otherwise have been possible. *Id.* at 178-179. The *Diehr* patent thus contained a great deal more than the Arrhenius equation itself. By contrast, in *Parker* v. *Flook*, 437 U.S. 584 (1978), the patent failed because, as this Court explained in *Diehr*, it merely recited a mathematical formula with "token postsolution activity." 450 U.S. at 193 n.14.

There can be no serious dispute about which side of the *Diehr-Flook* divide this case is on. From the standpoint of patent law, the correlation between level of total homocysteine and existence of a cobalamin or folate deficiency is equivalent to the Arrhenius equation. Both describe relationships in nature. See *Diehr*, 450 U.S. at 186. In other words, the correlation between elevated homocysteine levels and vitamin deficiency is something like an equation created by the biochemistry of humans and other species. On one side are measurable variables – the levels of homocysteine. On the other side is the variable of ultimate interest – the existence or not of a B vitamin deficiency.

The only information in claim 13 other than the unpatentable scientific relationship is the intellectually insignificant teaching that the quantities of one of the substances must be measured. It is as if, to borrow the *Diehr* context, the claim said only: "A method for calculating the rate of a chemical reaction consisting of (1) measuring the temperature of the reacting substances; and (2) entering the temperature into the Arrhenius equation." Such a claim obviously would fail; it contains in substance nothing other than the unpatentable law of nature. Claim 13 is no different.

The *Flook* patent was defective in part because it recited a mathematical formula without explaining how the values of the variables in that formula were to be determined. See *Diehr*, 450 U.S. at 186 & n.10. Claim 13 has the same fatal flaw. Because it allows the homocysteine assay to be performed by any means at all, it does not specify how the values of the measurable variables are to be determined. It simply recites the insignificant point that one must get those values before using the equation to derive the information of ultimate interest. Again, a great deal of ingenuity may be required to get those values, and testing methods reflecting such ingenuity are the subject of valid portions of the '658 patent and countless others. But claim 13 describes nothing of the kind.

Accordingly, even when claim 13 is viewed as a whole, it still fails to describe a "process" within the meaning of 35 U.S.C. § 101.

B. Claim 13 also runs afoul of the related principle that a "process" claim comprising every "substantial practical application" of a natural principle is invalid because "in practical effect" such a claim "would be a patent on the [natural principle] itself." *Gottschalk* v. *Benson*, 409 U.S. 63, 71-72 (1972).

The statistical relationship between levels of homocysteine and the existence of a cobalamin or folate deficiency has "no substantial practical application" other than to diagnose those deficiencies. This relationship by its nature can be used to determine one thing, and one thing only: the possible existence of a deficiency. But that is exactly how broad claim 13 is: it purports to describe a "method for detecting a deficiency of cobalamin or folate." In other words, the claim is tautological and therefore extends to every practical application of the natural relationship that it recites.

A useful analogy here is the "merger" doctrine in copyright law. An axiom of copyright is that it will not protect an idea, only the particular expression of an idea. 4 NIMMER ON COPYRIGHT § 13.03[B][2][a]; 17 U.S.C. § 102(b); cf. *Benson*,

409 U.S. at 71 ("It is conceded that one may not patent an idea."). However, when "a given idea is inseparably tied to a particular expression" such that "there is a 'merger' of idea and expression" – when, in other words, there is but one way of reducing the general idea to a particular expression – courts may deny copyright protection to the expression in order to avoid conferring a monopoly on the idea. 4 NIMMER § 13.03[B][3].

The *Benson* teaching is similar. Only an application of a natural principle may be patented; the principle itself is unprotectable. However, where a patent claims every application of a natural principle (as in copyright when an idea can be expressed in only one way), that patent is invalid (just as in copyright the expression is not protected) because the alternative is to preempt the principle itself (just as in copyright the alternative is to create a monopoly on the idea).

Claim 13 is barred by these principles. It is tautologically constructed so as to claim every conceivable practical application of the natural relationship it discloses: make (by any means) the measurement that correlates with a medical condition and then look at the results to decide whether the medical condition might exist. There is simply no way of applying the statistical correlation between the level of total homocysteine and a deficiency of cobalamin or folate that does not entail "detecting a deficiency [or not] of cobalamin or folate" – and claim 13 by its terms extends to all such acts of detection.

C. There is no merit to any argument that claim 13 is valid because the assay step might, as the United States suggested in its certiorari-stage brief, "entail significant physical or chemical alteration of a sample of blood or bodily fluid." U.S. Br. 9. That is an argument in favor of allowing *assaying techniques* to be patentable – as indeed respondents' technique for assaying homocysteine is. Claims 1 through 12 of the '658 patent are unchallenged here. But a claim that purports to exclude others from making, using, or selling the "invention" consisting of conducting *any* assay and then "correlating" the results stands on a different footing. It bears repeating that the alleged patent

infringers in this case are doctors who *used* the assay results, not petitioner, which performed the assays and is accused of inducing infringement by encouraging the doctors to use the natural relationship between elevated homocysteine levels and vitamin deficiencies in interpreting the assay results.

It is true that this Court has said that "the clue to the patentability of a process claim that does not include particular machines" is the "[t]ransformation and reduction of an article 'to a different state or thing.'" *Benson*, 409 U.S. at 70 (quoting *Cochrane* v. *Deener*, 94 U.S. 780, 788 (1877)). But that is far from a holding that any transformation or reduction automatically makes a process patentable.

In *Diehr*, this Court explained:

> [W]hen a claim containing a mathematical formula implements or applies that formula in a structure or process which, when considered as a whole, *is performing a function which the patent laws were designed to protect* (*e.g.*, transforming or reducing an article to a different state or thing), then the claim satisfies the requirements of § 101.

450 U.S. at 192 (emphasis added). The *Diehr* patent involved a series of steps amounting to a bona fide industrial process. A scientific principle – Arrhenius' equation – was used, but only in the service of a physical or chemical transformation – the curing of rubber. Claim 13 does precisely the reverse. Any chemical or physical transformation involved in the homocysteine assay is merely a means to the end of making a mental connection between levels of homocysteine and the existence of a vitamin deficiency. The entire purpose of the assay, and therefore any transformation it entails, is to collect information for use in the "correlating" step.

"Considered as a whole," therefore, claim 13 does not even come close to "performing a function which the patent laws were designed to protect" – although claims 1 through 12 of the same patent do. "Considered as a whole," claim 13 merely discloses a statistical relationship, albeit one with obvious

clinical relevance. Cf. *In re Warmerdam*, 33 F.3d 1354, 1360 (Fed. Cir. 1994) ("Warmerdam's argument that the claim implies physically measuring the contour of an object misses the point. As a whole, the claim involves no more than the manipulation of abstract ideas."); *In re Grams*, 888 F.2d 835, 840 (Fed. Cir. 1989) (rejecting patent claims where "[t]he sole physical process step" was performing poorly specified clinical tests on individuals to obtain data; court determined that "applicants are, in essence, claiming the mathematical algorithm"); *In re Meyer*, 688 F.2d 789, 794, 796 (C.C.P.A. 1982) (data-gathering step in claim that recited an algorithm did not satisfy 35 U.S.C. § 101). Because the patent laws were not "designed to protect" natural statistical relationships, the fact that the unspecified assay might involve some physical or chemical transformation is immaterial.

D. Unnecessarily broad language in several Federal Circuit cases is in tension with this Court's own precedents. Whatever the merits of those cases on their own facts, they do not provide legitimate support for the conclusion that claim 13 of the '658 patent describes a patentable process. The Federal Circuit has recently suggested that, for a mathematical algorithm "to be patentable," it need only "be applied in a 'useful' way," *State Street Bank & Trust Co.* v. *Signature Fin. Group, Inc.*, 149 F.3d 1368, 1373 (Fed. Cir. 1998); accord *AT&T Corp.* v. *Excel Comm'ns, Inc.*, 172 F.3d 1352, 1357 (Fed. Cir. 1999), or "produce[] 'a useful, concrete and tangible result,'" *State Street Bank & Trust Co.*, 149 F.3d at 1373 (quoting *In re Alappat*, 33 F.3d 1526, 1544 (Fed. Cir. 1994) (en banc)); accord *AT&T Corp.*, 172 F.3d at 1357. There are at least three reasons why the statements in these cases should not be applied to save claim 13.

First, these cases are addressed only to the troublesome subject of inventive algorithms implemented on a computer, as opposed to the kind of naturally occurring phenomena at issue here. Such algorithms are typically the product of technical ingenuity rather than simply a discovery of a relationship in

nature. Indeed, the patents at issue in the Federal Circuit cases have little in common with claim 13. The *State Street Bank & Trust Co.* patent was titled "Data Processing System for Hub and Spoke Financial Services Configuration." It was directed to an intricate investment system – implemented with a complex computer program – whereby mutual funds pool their assets in a portfolio organized as a partnership in order to reduce administrative expenses but gain the tax advantages of a partnership. 149 F.3d at 1370. The *AT&T Corp.* patent was titled "Call Message Recording for Telephone Systems." It disclosed a method for aiding long-distance telephone companies in their billing by allowing the computerized data-recording systems in the public telephone network to identify the long-distance carriers associated with the calling and called parties. 172 F.3d at 1353-1355. And the *Alappat* patent was drawn to a method for processing the input signals to a digital oscilloscope so as to generate a smooth waveform on the display. 33 F.3d at 1537-1539.

Second, even if it were appropriate to apply the Federal Circuit's recent cases on computer-implemented algorithms to claim 13, claim 13 still would fail because it does not disclose "a useful, concrete and tangible result." The only "result" in claim 13 is the ability to diagnosis a vitamin B deficiency – in other words, to apply the very natural correlation disclosed in the claim. This sort of tautology is a far cry from the tangible results in the Federal Circuit cases reviewed above – a novel investment structure that achieves significant cost savings, a key signpost in the electronic traffic that eventually resolves itself into long-distance telephone bills, and a better oscilloscope display.

Finally, to apply the Federal Circuit's standards for computer-implemented algorithms and hold that claim 13 satisfies them would produce a result in conflict with this Court's precedents. Such a holding would essentially say that a natural relationship *can* be patented, so long as it is paired with at least one practical application, no matter how little

inventive content there is in the pairing. As *Diehr*, *Flook*, and *Benson* make clear, that is not the law.

CONCLUSION

The judgment of the court of appeals should be reversed.

Respectfully submitted.

ROY T. ENGLERT, JR.*
DANIEL WALFISH
Robbins, Russell, Englert, Orseck & Untereiner LLP
1801 K Street, N.W.
Suite 411
Washington, D.C. 20006
(202) 775-4500

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* *Counsel of Record*

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IN THE

Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS, dba LabCorp,

Petitioner,

v.

METABOLITE LABORATORIES, INC., *et al.*,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF *AMICUS CURIAE* AMERICAN EXPRESS COMPANY IN SUPPORT OF NEITHER PARTY

RAYMOND MILLIEN
AMERICAN EXPRESS
200 Vesey Street
New York, NY 10285
(212) 640-1219

ABBE DAVID LOWELL
Counsel of Record
JOSEPH A. CALVARUSO
WALTER G. HANCHUK
RICHARD MARTINELLI
CHADBOURNE & PARKE LLP
30 Rockefeller Plaza
NEW YORK, NY 10112
(212) 408-5100

Counsel for Amicus Curiae

198578

COUNSEL PRESS
(800) 274-3321 • (800) 359-6859

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INTEREST OF *AMICUS CURIAE*[1]

American Express Company ("AmEx"), founded in 1850, is a leading global payments, network and travel company. AmEx offers a broad range of products including charge and credit cards; stored value products such as Travelers Cheques, Travelers Cheque funds cards and gift cards; travel agency services and travel, entertainment and purchasing expense management services; network services and merchant acquisition and merchant processing for network partners and proprietary payments businesses. AmEx's various products are sold globally to diverse customer groups, including consumers, small businesses, mid-market companies, large corporations and banking institutions. These products are sold through various channels including direct mail, on-line applications, targeted sales-forces and direct response advertising.

AmEx holds many patents and, in recent years, has filed hundreds of patent applications with the United States Patent and Trademark Office (USPTO). Many of these patents and patent applications are classified by the USPTO as being in Class 705 "Data Processing: Financial, Business Practice, Management, Or Cost/Price Determination," which includes, *inter alia*, what many refer to as "Business Method Patents." Over the years, AmEx has made substantial investments to protect its intellectual property via the patent system. AmEx's substantial investment benefits both itself and the public.

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1. Pursuant to Supreme Court Rule 37.6, *amicus* states that no counsel for a party authored this brief in whole or in part and no person or entity, other than *amicus*, or its counsel made a monetary contribution to the preparation or submission of this brief. Letters from all parties consenting to the filing of this brief are being submitted herewith.

See Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 63, (1998) ("[T]he patent system represents a carefully crafted bargain that encourages both the creation and the public disclosure of new and useful advances in technology, in return for an exclusive monopoly for a limited period of time.").

This Court last addressed the scope of patentable subject matter under 35 U.S.C. § 101 in *Diamond v. Diehr*, 450 U.S. 175 (1981). In the 24 years since that decision, technology has advanced at a frenetic pace. U.S. patent law has similarly evolved to embrace these advances. As is often the case, however, progress begets controversy. For example, the Federal Circuit's decisions in *State Street Bank & Trust Co. v. Signature Fin. Group, Inc.*, 149 F.3d 1368, 1375 (Fed. Cir. 1998), *cert. denied*, 525 U.S. 1093 (1999) (taking the "opportunity to lay this ill-conceived [business method] exception to rest"), and *AT&T Corp. v. Excel Communications, Inc.*, 172 F.3d 1352, 1356 (Fed. Cir. 1999), *cert. denied*, 528 U.S. 946 (1999) (holding that "the judicially-defined proscription against patenting of a 'mathematical algorithm,' to the extent such a proscription still exists, is narrowly limited to mathematical algorithms in the abstract"), have engendered spirited debate over the scope of § 101 in the popular press, the business community (especially the financial services industry), Congress, the USPTO and members of the Patent Bar, as well as the legal community at large.

In advocating a challenge to the breadth of patentable subject matter provided by this precedent, some commentators have suggested, and *amici curiae* may assert, that the present case provides a vehicle to address the full scope of patentability provided by the current law, including

the patentability of so-called "Business Method Patents."[2] The present case, however, is unrelated to so-called "Business Method Patents" and ultimately turns on the scope of the law of nature and natural phenomena exceptions to patentability under § 101. AmEx takes no position as to who should prevail in the current action, nor does it take a position on the ultimate limits of the law of nature and natural phenomena exceptions. AmEx's only interest is in ensuring that the Court appreciates that the facts and issues presented in this case do not implicate the broader aspects of § 101, nor do they provide an appropriate basis for articulating rules that would implicate the patentability of claims that are not directed to a law of nature or natural phenomena, such as so-called "Business Method Patents."

SUMMARY OF ARGUMENT

The only issue raised by the present case is whether Claim 13 of LabCorp's patent impermissibly claims a law of nature or natural phenomena. This case is not relevant to any other exception to the broad scope of patentable subject matter available under § 101. The law of nature and natural phenomena exceptions have often been discussed collectively with a different exception to § 101 that prevents the patenting of abstract ideas. Close review of the case law, however, demonstrates that the law of nature and natural phenomena exceptions are, in fact, distinct from the abstract ideas exception. The law of nature and natural phenomena exceptions serve policy considerations unrelated to the policy

2. The temptation to expand the issues presented in the current case is probably exacerbated somewhat because the Federal Circuit did not address the § 101 issue below and, therefore, did not provide an opinion that in any way framed the issue of the proper scope of § 101.

considerations served by the abstract ideas exception. While AmEx does not express an opinion as to the appropriate outcome of this case, it strongly believes that the *only* issue before the Court is whether LabCorp's Claim 13 improperly preempts a law of nature or natural phenomena.

ARGUMENT

By its express language, § 101 of the patent law provides a broad definition of patentable subject matter. *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980) ("Congress plainly contemplated that the patent laws would be given wide scope."). The statute provides that a patent may be granted for "*any* . . . process, machine, manufacture, or composition of matter. . . ." 35 U.S.C. § 101 (*emphasis added*). The scope of § 101, however, is not unbounded. Supreme Court precedent dictates the outside limits of patentability. As articulated most recently by this Court in *Diehr*, "[e]xcluded from . . . patent protection are laws of nature, natural phenomena, and abstract ideas." 450 U.S. at 185. Indeed, the Court specifically identified this standard in requesting the Acting Solicitor General's view regarding LabCorp's *certiorari* petition. *Laboratory Corp. v. Metabolite Labs., Inc.*, 125 S. Ct. 1413, 1414 (Feb. 28, 2005).

In practice, the *Diehr* standard articulates two distinct and separate limits on patentability under § 101, one to laws of nature and natural phenomena, and the other to abstract ideas.[3]

3. Although *Diehr* lists laws of nature and natural phenomena as two separate exclusions, the Court has used these terms interchangeably. In *Le Roy v. Tatham*, 55 U.S. 156, 175 (1852), the Court stated that a "power in nature" cannot be patented. Almost a (Cont'd)

The law of nature and natural phenomena exceptions are premised on the idea that such discoveries are "manifestations of . . . nature, free to all men and reserved exclusively to none." *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948). Accordingly, otherwise patentable claims will fail if they preempt all practical application of a law of nature or natural phenomena. In *Funk Bros.*, for example, the patentee discovered and claimed a plant incoculant containing a combination of naturally occurring bacteria in which the various strains of bacteria functioned without inhibiting each other. *Id.* at 128. This Court held that the patentee's "invention" was no more than a claim to the discovery that certain bacteria strains possess natural qualities of non-inhibition. *Id.* at 131.

The law of nature and natural phenomena exceptions serve the important public policy of keeping the basic foundations of scientific research and its technical application available for others to use and build upon. *Le Roy v. Tatham*, 55 U.S. 156, 175 (1852). "Thus, a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity." *Diamond v. Chakrabarty*, 447 U.S. at 309.

(Cont'd)

century later, the Court introduced the term "phenomena of nature" when it cited *Le Roy* for the principle that "patents cannot issue for the discovery of the phenomena of nature." *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948). Subsequently, the phrases "laws of nature" and "natural phenomena" were recited independently when framing the exception, without any apparent distinction in their scope.

In contrast to the law of nature and natural phenomena exceptions, the abstract ideas exception excludes inventions that are claimed in a way that is not bounded by practical application. In performing this analysis, like most all patent analyses, the scope and content of the claim is the key. Claims to abstract ideas constitute disembodied concepts, which alone are not "useful" from a practical stand point, *i.e.*, they are not "useful" until reduced to a practical application. *In re Alappat*, 33 F.3d 1526, 1543 (Fed. Cir. 1994) (en banc). For example, in *Le Roy* this Court held, "[a] principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented, as no one can claim in either of them an exclusive right. . . ." *Le Roy*, 55 U.S. at 175.

The different issues underlying the law of nature and natural phenomena exceptions and the abstract ideas exception dictate different analyses and policy concerns. The rationale behind the law of nature and natural phenomena exceptions is that otherwise patentable subject matter should be excluded from patentability if it preempts *all* use of a law of nature or natural phenomena. The test for patentability under this restriction, therefore, focuses on defining the natural law at issue and the consequences and extent of any preemption caused by the subject claims.

In contrast, a preemption analysis is not helpful in analyzing the abstract ideas exception because almost every invention can be boiled down to an idea. The key is whether the claim recites a useful and practical application of the idea. For example, in *Dolbear v. American Bell Tel. Co.*, 126 U.S. 1, 535 (1888), this Court responded to a challenge to Alexander Graham Bell's claim for a "method of and apparatus for transmitting vocal or other sounds

telegraphically, as herein described, by causing electrical undulations . . ." and held:

> It may be that electricity cannot be used at all for the transmission of speech, except in the way Bell has discovered, and that therefore, practically, his patent gives him its exclusive use for that purpose; but that does not make his claim one for the use of electricity distinct from the particular process with which it is connected in his patent. *It will, if true, show more clearly the great importance of his discovery, but it will not invalidate his patent.*

(*emphasis added*). *Dolbear* recognizes that an inventor should not be punished for fully comprehending and explaining the broad applicability of his invention. Of course, a claim's breadth is always subject to the strictures of 35 U.S.C. §§ 102, 103 and 112.[4] In practice, applying a preemption test to abstract ideas would also burden the patentee with the inequitable task of proving that there are uses of the patentee's ideas *not* preempted by the patent. Aside from the difficulty of proving a negative, the test would essentially obligate the patentee to invent, but not claim, those additional uses to overcome a challenge to the patent. The impracticality of such a test is also demonstrated by the fact that additional uses of an abstract idea will most likely develop over time due to advances in other aspects and areas of technology. Accordingly, an abstract idea preemption analysis would vary depending on the state of the art at the time the analysis is made.

---

4. *See Diehr*, 450 U.S. at 191 (a later determination finding a lack of novelty under § 102 or obviousness under § 103 does not affect the determination of eligibility for patent protection under § 101).

Turning to the present facts before the Court, Claim 13 of LabCorp's patent reads:

> A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> assaying a body fluid for an elevated level of total homocysteine; and
>
> correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

The claim is certainly not an abstract idea because it is directed to a useful and practical end, *i.e.*, diagnosing vitamin deficiencies that could lead to serious medical conditions in a patient. The claim may raise an issue regarding its preemption of a law of nature or natural phenomena. For example, the law of nature or natural phenomena at issue in Claim 13 could be stated as either: (1) the relationship between elevated total homocysteine and a cobalamin or folate deficiency; or, (2) that cobalamin and folate are required to metabolize homocysteine. AmEx, however, offers no opinion as to whether Claim 13 impermissibly claims a law of nature or natural phenomena.

CONCLUSION

While AmEx offers no opinion as to the outcome of the current patentability analysis, AmEx does believe that this case only implicates the law of nature and natural phenomena exceptions to § 101. Moreover, while the abstract ideas exception may be more broadly applicable to all types of claims, it is founded on distinct bases and rationales irrelevant to the law of nature and natural phenomena exceptions currently before the Court. The bottom line is that the record in the present case is devoid of any facts or issues that would implicate the full scope of patentability under § 101, including claims not directed to a law of nature or natural phenomena, such as so-called "Business Method Patents."

Respectfully submitted,

ABBE DAVID LOWELL
Counsel of Record
JOSEPH A. CALVARUSO
WALTER G. HANCHUK
RICHARD MARTINELLI
CHADBOURNE & PARKE LLP
30 Rockefeller Plaza
NEW YORK, NY 10112
(212) 408-5100

RAYMOND MILLIEN
AMERICAN EXPRESS
200 Vesey Street
New York, NY 10285
(212) 640-1219

Counsel for Amicus Curiae

(22)

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IN THE

Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS (DOING BUSINESS AS LABCORP),

Petitioner,

v.

METABOLITE LABORATORIES, INC., and COMPETITIVE TECHNOLOGIES, INC.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF THE AMERICAN HEART ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

DAVID WM. LIVINGSTON
EXECUTIVE VICE PRESIDENT, CORPORATE SECRETARY & GENERAL COUNSEL
AMERICAN HEART ASSOCIATION
7272 Greenville Avenue
Dallas, Texas 75231-4596
(214) 706-1246

GREGORY A. CASTANIAS
(*Counsel of Record*)
51 Louisiana Avenue, N.W.
Washington, D.C. 20001-2113
(202) 879-3939

Counsel for Amicus Curiae

WILSON-EPES PRINTING CO., INC. – (202) 789-0096 – WASHINGTON, D. C. 20001

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STATEMENT OF INTEREST*

Amicus, the American Heart Association ("AHA"), is a nonprofit, national voluntary health organization with the mission of reducing disability and death from cardiovascular diseases and stroke. AHA's strategic goal, adopted in 1998, is to positively affect the general health and well-being of American society by helping to reduce cardiovascular diseases, stroke, and risk by 25 percent by 2010. This bold strategic goal responds to the sobering reality that as many as 930,000 of our fellow Americans—family, friends, and neighbors—are killed every year by these diseases, and many thousands more are disabled. Heart attacks and strokes devastate victims, families, and relationships, threatening life and bringing emotional upheaval and financial distress to all segments of American society.

Research shows that coronary heart disease, stroke, and risk can be best prevented if Americans take charge of their own health in close consultation with healthcare providers. AHA promotes individual healthcare responsibility by publishing guidelines regarding practical, sensible ways to protect health, advising Americans as to the risks of poor health, and teaching patients how to reduce those risks in partnership with their healthcare providers.

The AHA has no interest in taking sides in a commercial patent dispute. However, because the Court's decision in this case will have profound effects on the way in which healthcare professionals are able to render healthcare advice to patients dealing with cardiovascular diseases and stroke (among other disorders), *amicus* has a special interest in participating in the debate over whether a patent claim, which claims a simple two-step method for correlating test

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* No party other than *amicus* and its counsel authored this brief in whole or in part, and no person or entity, other than *amicus* and its counsel, has made a monetary contribution to the preparation or submission of this brief. Both parties have granted consent to the filing of this *amicus curiae* brief. Letters of consent are on file with the Clerk of the Court.

results using a basic, known scientific relationship, can trigger the exclusionary power of a United States patent so as to prohibit a physician from dispensing cardiovascular-related and other healthcare advice to patients. In addition, *amicus* holds a special position in the community of individuals affected by this patent in view of its interest in promulgating research and encouraging health testing, and is uniquely suited to provide the Court with what *amicus* believes will be helpful insights into the impact of this case on the healthcare profession and the patients served by that profession.

STATEMENT

1. Since the 1960s, epidemiological studies have shown a relationship between elevated blood levels of the amino acid homocysteine and the risk of coronary heart disease, stroke, and peripheral vascular disease. *See* Peter W. F. Wilson, *Homocysteine and Coronary Heart Disease*, 288 J. AM. MED. ASSOCIATION 2042, 2042-43 (2003). Plasma homocysteine levels are strongly influenced by diet, as well as genetic factors. The dietary components with the greatest effects are folic acid and vitamins B_6 and B_{12}, the latter of which contains the element cobalt and is thus known as cobalamin. Because the B vitamins assist in metabolizing homocysteine, scientists can directly assay homocysteine, along with other substances, in plasma to screen for cobalamin and folate deficiency. There are, in addition, multiple other reasons for plasma homocysteine levels to be elevated. *See generally* Ralph Carmel *et al.*, *Update on Cobalamin, Folate, and Homocysteine*, 2003 HEMATOLOGY 62, 62-81 (2003).

2. In the 1980s, scientific researchers at University Patents Inc. ("UPI"), the predecessor of respondent Competitive Technologies, Inc. ("CTI"), discovered that elevated levels of total homocysteine are closely associated with deficiencies in cobalamin or folate. UPI scientists applied for and received U.S. Patent No. 4,940,658 ("the

'658 patent"), which contains claims drawn to methods for assaying samples of body tissues to determine total homocysteine levels, as well as methods for both diagnosing and treating cobalamin and folate deficiency based on elevated total homocysteine. Pet. App. 2a-3a. Claim 13 of the '658 patent, at issue here, identifies a two-step "method for detecting a deficiency of cobalamin or folate in warm-blooded animals," comprising the following steps:

> assaying a body fluid for an elevated level of total homocysteine; and
>
> correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

Id. at 3a.

3. CTI licensed the '658 patent to respondent Metabolite Laboratories, Inc. ("Metabolite"), which in turn sub-licensed the patent to the predecessor-in-interest of petitioner Laboratory Corporation of America Holdings ("LabCorp"). Physicians ordered total homocysteine assays from LabCorp, which initially performed the assays under its sub-license by using the assay method set forth in the patent. In 1998, however, LabCorp began using a different assay method and stopped paying royalties to Metabolite. Metabolite then filed suit against petitioner for inducing patent infringement by the physicians and for breach of contract. *Id.* at 3a-4a.

4.a. Metabolite sued LabCorp for direct and indirect infringement of the '658 patent (and for breach of the sub-license agreement), alleging that LabCorp's performance of homocysteine tests using the alternative method induced and contributed to doctors' infringement of claim 13 of that patent. *Id.* The district court, pursuant to *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996), issued a pre-trial order construing claim 13. The court defined "elevated" as "raised above the normal range." Pet. App. 29a, 32a. The court also defined "correlating" as meaning

"to establish a mutual or reciprocal relationship." *Id.* at 29a. Having construed the disputed claim terms, the case proceeded to trial before a jury. The jury returned a verdict against LabCorp for contributory and induced infringement, and for breach of the sub-license agreement. The jury assessed damages against LabCorp in the amount of $3,652,724.61 for breach of contract and $1,019,365.01 for infringement. *Id.* at 4a. The jury also found LabCorp's infringement to be willful, and returned a verdict in favor of plaintiffs on LabCorp's invalidity defenses. The district court entered judgment against LabCorp and awarded damages as assessed by the jury. *Id.* at 34a-39a.

b. After the trial, the district court denied LabCorp's motion for judgment as a matter of law on infringement, breach of contract, patent invalidity, and willful infringement. In light of the finding of willful infringement, the district court doubled the jury's infringement award to $2,038,730.02. *See* 35 U.S.C. § 284 (second paragraph). The district court also permanently enjoined LabCorp from using the alternative homocysteine-only test. Pet. App. at 34a-39a. LabCorp appealed.

c. A divided panel of the Federal Circuit affirmed. *Id.* at 1a-27a. Focusing on the correlating step of claim 13, the court of appeals held that "'correlating' means to relate the presence of an elevated total homocysteine level to either a cobalamin or folate deficiency, or both . . . and also to relate the absence of an elevated total homocysteine level to a deficiency in neither." *Id.* at 12a. Because "[t]he record shows that physicians order assays and correlate the results of those assays," the court of appeals held that physicians who ordered assays from petitioner after petitioner stopped making royalty payments had directly infringed the patent. *Id.* at 13a. The court further concluded that substantial evidence supported the jury's finding that petitioner intended to induce such infringement because petitioner provided total homocysteine assays to physicians, and encouraged the use of such assays to detect cobalamin and folate deficiency by

publishing and providing articles setting forth the correlation between elevated total homocysteine levels and cobalamin and folate deficiency. *Id.* at 15a.

The court of appeals rejected LabCorp's contentions that claim 13 is invalid on grounds of indefiniteness, lack of written description and enablement, anticipation, and obviousness. *Id.* at 15a-21a. In the course of rejecting LabCorp's anticipation and obviousness challenges to claim 13, the Federal Circuit specifically noted:

> In this case, the correlating step does not require computer technology or extensive computations. Instead, the record shows repeatedly that the correlating step is well within the knowledge of one of skill in this art. The correlating step is a simple conclusion that a cobalamin/folate deficiency exists *vel non* based on the assaying step.

Id. at 18a.

Judge Schall concurred in part and dissented in part. *Id.* at 28a-33a. He "agree[d] with the majority's conclusions with respect to validity" of the patent, but would have construed claim 13 more narrowly than did the district court and the panel majority. *Id.* at 28a. Because "[t]he plain language of the claim requires 'elevated' levels of homocysteine," Judge Schall concluded that claim 13 is infringed only when a test reveals elevated levels, not when it reveals normal or low levels. *Id.* at 30a.

The Federal Circuit denied LabCorp's petition for rehearing and rehearing *en banc*. *Id.* at 40a-41a.

d. After calling for the views of the Solicitor General, this Court granted certiorari limited to question three of the Petition: "Whether a method patent setting forth an indefinite, undescribed, and non-enabling step directing a party simply to 'correlat[e]' test results can validly claim a monopoly over a basic scientific relationship used in medical treatment such that any doctor necessarily infringes the

patent merely by thinking about the relationship after looking at the test result." 126 S. Ct. 601 (2005).

SUMMARY OF ARGUMENT

In this case, the Court is asked to resolve the extent of patentable subject matter under the Constitution and patent laws of the United States. The starting point for addressing this question is the basic truth that only inventions are patentable; laws of nature are not. Careful scrutiny of this principle, from this Court's earliest patent cases, *O'Reilly v. Morse*, 56 U.S. (15 How.) 62 (1853), and *The Telephone Cases*, 126 U.S. 1 (1888), through this Court's more recent pronouncements, *Parker v. Flook*, 437 U.S. 584 (1978), and *Diamond v. Diehr*, 450 U.S. 175, 185 (1981), limns the following rule: "[Patent] claims which *directly or indirectly preempt* natural laws or phenomena are proscribed, whereas claims which merely *utilize* natural phenomena via explicitly recited manufactures, compositions of matter or processes to accomplish new and useful end results define statutory inventions." *In re Bergy*, 596 F.2d 952, 988 (C.C.P.A. 1979) (Rich, J.), *vacated as moot*, 444 U.S. 1028 (1980) (emphasis added).

Application of this Court's existing precedent to claim 13 easily yields the conclusion that it contains nothing inventive. Rather, it seeks to claim a private right to exclude all others from utilizing a scientific correlation that the named inventors did not "invent."

If claim 13 of the '658 patent were held by this Court to cover patentable subject matter, it would grant respondents an exclusionary right that would prevent doctors from properly diagnosing and treating cardiovascular disease risk in their patients, not to mention other disorders—including even cobalamin (vitamin B_{12}) deficiency itself. It would forbid physicians from following the AHA's published Science Advisory for physicians in the course of patient treatment. And it would surely open the floodgates to a spate of similar patent applications in other areas of medical

diagnosis and treatment. The Court should maintain the proper balance in this area by reversing the judgment of the Federal Circuit and holding that claim 13 of the '658 patent claims no "invention" within the meaning of the Constitution and Patent Act.

ARGUMENT

U.S. Letters Patent 4,940,658, entitled "Assay for Sulfhydryl Amino Acids and Methods for Detecting and Distinguishing Cobalamin and Folic Acid Deficiency," contains 34 method claims. Claims 1-12 are drawn to particular methods of "assaying for the amount of one or more sulfhydryl amino acid species present in a given sample" (S.A. 30, column 41, lines 2-4); claims 13-28, 33, and 34 are drawn to methods for "detecting a deficiency of cobalamin or folate in warm-blooded animals" (*e.g.*, S.A. 30, column 41, lines 58-59); and claims 29-32 are drawn to methods of "treating a human for cobalamin deficiency" or "folic acid deficiency" (S.A. 31, column 43, lines 29-30; *id.*, column 44, lines 10-11, 17-18.)

This case involves independent claim 13 of the '658 Patent. That claim is a broadly drafted, two-step

> method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> [1] assaying a body fluid for an elevated level of total homocysteine; and
>
> [2] correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

S.A. 30, column 41, lines 58-65 (bracketed numbers added).

As to the first claimed step of "assaying," claim 13 is not, by its terms, limited to any particular type of assay. Other claims (14-17 and 19-28) *do* specify the type of assay required, however. *See* S.A. 30, column 42, lines 7-25; *id.*, column 42, line 37 to column 43, line 28. And as to the

second step of "correlating," both the district court and the Federal Circuit gave this claim step an exceedingly broad reading, concluding that it "only requires association of homocysteine levels with vitamin deficiencies. It requires no further correlation to confirm the relationship to vitamin deficiencies." Pet. App. 8a; *see also* J.A. 58-61 (district court *Markman* order). "The correlating step is a simple conclusion that a cobalamin/folate deficiency exists *vel non* based on the assaying step." Pet. App. 18a.

It is against this backdrop that this Court must consider the question presented.

I. CLAIM 13 OF THE '658 PATENT IMPROPERLY ATTEMPTS TO PATENT A LAW OF NATURE: THE BASIC, KNOWN NATURAL CORRELATION BETWEEN HOMOCYSTEINE AND B VITAMINS

A. Only "Inventions" Are Patentable; Laws Of Nature Are Not

The starting point for addressing the question presented in this case is the bargain struck by the Patent Clause of the Constitution: "The Congress shall have Power . . . To Promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries . . . ." U.S. CONST., art. I, § 8, cl. 8. The Constitution thus empowers Congress only to reward "Inventors" with an exclusionary right of limited term for their inventions. That right to exclude "is a property right; and like any property right, its boundaries should be clear." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722, 731 (2002). In keeping the boundaries of the right clear, the Constitution requires that the patent laws "Promote," rather than inhibit, the "Progress of Science and useful Arts" for the public interest. The constitutional requirement of "invention" is implemented by Section 101 of the Patent Act, whereby a patent may be granted to "[w]ho[m]ever invents

or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." 35 U.S.C. § 101.

Under the Constitution and the Patent Act, it is necessary—but not sufficient—that the applicant have made a "discovery" in order to obtain a patent. "Invention," too, is required.

> A discovery may be brilliant and useful, and not patentable. No matter through what long, solitary vigils, or by what importunate efforts, the secret may be wrung from the bosom of Nature, or to what useful purpose it may be applied. Something more is necessary. The new force or principle brought to light must be embodied and set to work, and can be patented only in connection or combination with the means by which, or the medium through which, it operates.

Morton v. New York Eye Infirmary, 5 Blatchf. 116, 17 F. Cas. 879, 884 (C.C.N.Y. 1862). Thus, as this Court stated in *Thompson v. Boisselier*, the beneficiary of a patent "must be an inventor *and* he must have made a discovery. The statute has always carried out this idea." 114 U.S. 1, 11 (1885) (emphasis added).

"The rule that the discovery of a law of nature cannot be patented rests, not on the notion that natural phenomena are not processes, but rather on the more fundamental understanding that they are not the kind of 'discoveries' that the statute was enacted to protect." *Parker v. Flook*, 437 U.S. 584, 593 (1978). Careful scrutiny in this area is essential to the public interest, given "that scientific principles and laws of nature, even when for the first time discovered, have existed throughout time, define the relationship of man to his environment, and, as a consequence, ought not to be the subject of exclusive rights of any one person." *In re Meyer*, 688 F.2d 789, 795

(C.C.P.A. 1982) (citing *Le Roy v. Tatham*, 55 U.S. (14 How.) 156, 175 (1852)).

The additional requirement of "invention" ensures, among other things, that individuals cannot obtain exclusionary rights for fundamental scientific truths which existed *a priori*, but were "discovered" through exercise of the scientific act. That is why it is a commonplace that "[p]henomena of nature, though just discovered . . . are not patentable, as they are the basic tools of scientific and technological work." *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972); *see also Diamond v. Diehr*, 450 U.S. 175, 185 (1981) ("laws of nature, natural phenomena, and abstract ideas" are not patentable subject matter).* "[T]he discovery of [a natural] phenomenon cannot support a patent unless there is some other inventive concept in its application." *Parker v. Flook*, 437 U.S. at 594; *see also* 1 ERNEST B. LIPSCOMB, WALKER ON PATENTS § 2:3, at 102 (3d ed. 1985) ("There must not only be an addition to knowledge but there must be produced as the result of the exercise of the inventive faculties a new and useful thing or result or a new process of producing an old thing or result."). In other words, patents are issued to "Inventors" only for their work in bringing about new means—inventions—to achieve certain useful ends.

B. Where A Patent Claim Would Confer A Private Property Right On All, Or A Substantial Part, Of A Natural Law Or Phenomenon, It Is Invalid

It is easy to state the principle that laws of nature or natural phenomena are not patentable, while inventions that merely utilize such scientific truths are patentable. Yet, "the

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* *Accord, e.g., Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980); *Parker v. Flook*, 437 U.S. 584, 589 (1978); *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948); *Mackay Radio & Tel. Co. v. Radio Corp. of Am.*, 306 U.S. 86, 94 (1939); *Le Roy v. Tatham*, 55 U.S. (14 How.) 156, 175 (1852); *Wall v. Leck*, 66 F. 552, 558 (9th Cir. 1895).

line between a patentable 'process' and an unpatentable 'principle' is not always clear." *Parker v. Flook*, 437 U.S. at 589. The harder question arises when a patent claim that purports to go beyond the scientific truth itself nonetheless threatens to grant private exclusionary rights over many (or any) uses of that scientific truth. *See, e.g.*, Stephen G. Breyer, *Genetic Advances and Legal Institutions*, 28 J. L. MED. & ETHICS 23, 27 (2000) ("The most difficult question is deciding [whether] products of [] research reflect only discovery of an existing aspect of nature, like Einstein's discovery of the principles of relativity, [or whether] they amount to a protectable invention or useful device."); GEORGE T. CURTIS, A TREATISE ON THE LAW OF PATENTS FOR USEFUL INVENTIONS § 124 (4th ed. 1873) (describing the question as "how far a discovery or invention which may first disclose and practically embody some truth in physics or some law in the operation of the forces of nature, for a useful purpose, is capable of being carried in the exclusive privileges secured by the grant of letters patent"). The proper answer to this question should be this: Where a patent claim would confer a private exclusionary right on all, or a substantial part of, a natural phenomenon or law of nature, it is invalid.

William C. Robinson's seminal 1890 treatise described the nature of the inventive act and exhaustively explored the bases for the prohibition against patenting laws of nature or natural phenomena. 1 ROBINSON ON PATENTS §§ 133-143 (1890). Robinson recognized, over a hundred years ago, the line between laws of nature and inventions that merely employ those laws:

> In one sense, the word "principle" denotes the physical force employed by an invention. The other appellations given to this force are very numerous, and most of them are wholly inappropriate. It has been called "an elementary truth," "a principle of science," "a property of matter," "a law of nature," the "root and ground of science;" but the idea which

> underlies these phrases is sufficiently apparent, and is neither less nor more than that of some natural power or energy, which operates with uniformity under given circumstances, and may thus be contemplated as obedient to law. A principle, in this sense, is a necessary factor in every means which produces physical effects, whether such means be natural or artificial, and it is generally this which makes the chief impression on the senses of the observer; but it is in itself no true invention, nor can it be protected by a patent.

Id. § 135, at 193-95 (emphasis added) (footnote omitted).

Two cases decided by this Court in the years leading up to Robinson's treatise serve as the polestars that have long defined the line between patentable and unpatentable subject matter where laws of nature or natural phenomena are involved.

At one end of the spectrum, and helping to define the scope of what is not patentable, is the landmark Telegraph Case, *O'Reilly v. Morse*, 56 U.S. (15 How.) 62 (1853). There, Samuel Morse had received a patent for an apparatus for accomplishing the transmission of signals from a distance to an electromagnetic telegraph. *Id.* at 63. When Morse sued for patent infringement, the patent was challenged as not drawn to patentable subject matter. *Id.* In the Eighth Claim of the patent, Morse claimed rights to all uses of electromagnetism for sending signals over distance:

> Eighth. I do not propose to limit myself to the specific machinery or parts of machinery described in the foregoing specification and claims; the essence of my invention being the use of the motive power of the electric or galvanic current, which I call electro-magnetism, *however developed*, for marking or printing intelligible characters, signs, or letters at any

> distance, being a new application of that power of which I claim to be the first inventor or discoverer.

Id. at 112 (emphasis added).

This Court held the Eighth Claim invalid, because it was not limited to the actual machinery Morse invented, but was instead drawn to give Morse exclusionary rights over the work of others as they subsequently employed the principle of electromagnetism in various machines and processes. *See id.* ("It is impossible to misunderstand the extent of this claim. [Morse] claims the exclusive right to every improvement . . . ."). As this Court noted, if such a claim were to

> be maintained, it matters not by what process or machinery the result is accomplished. For aught that we know of some future inventor, in the onward march of science, may discover a mode . . . without using any part of the process or combination set forth in the plaintiff's [claim] . . . But yet if it is covered by this patent the inventor could not use it, nor the public have the benefit of it without the permission of the patentee. . . . [Such a claim would amount to] an exclusive right to use a manner and process which he has not described and indeed had not invented, and therefore could not describe when he obtained his patent.

Id. at 113. Morse's Eighth Claim was thus struck down as improperly seeking an exclusionary property right in all uses of the underlying natural phenomenon of electromagnetism, not in his specific invention itself.

At the other end of the spectrum, and helping to define when merely using natural phenomena as a portion of an invention *is* patentable, is this Court's decision, twenty-five years later, in *The Telephone Cases*, 126 U.S. 1 (1888). Those cases involved the patentability of Alexander Graham Bell's invention, the telephone. Bell had discovered how to use electrical current to transmit voice signals by means of a

device that turned sound waves into electrical current, which was then transmitted over distance to a decoding device that transformed the waves back into sound. *Id.* at 531-35. Bell's Fifth Claim sought to patent "[t]he method of, and apparatus for, transmitting vocal or other sounds telegraphically, *as herein described*, by causing electrical undulation, similar in form to the vibrations of the air accompanying the said vocal or other sounds, substantially set forth [in the patent]." *Id.* at 531 (emphasis added).

Bell's opponents urged that he was—like Morse's Eighth Claim, *Morse*, 56 U.S. (15 How.) at 112—seeking to patent the essential mechanism of converting electricity into sound for all applications and with all devices. *The Telephone Cases*, 126 U.S. at 531. This Court held, however, that Bell was not claiming all uses of electricity converted to sound waves; rather, he was merely claiming the particular art, set forth in his patent, that utilized the principle of "controlling the force [of electricity] as to make it accomplish the purpose" of transmitting speech. *Id.* at 534. Bell was thus not claiming the principle itself, but was claiming his particular method and apparatus for utilizing that principle in a new and useful way. This Court decided that, because of the limiting clause in the claim—"as herein described"—the claim was necessarily cabined by Bell's apparatus. This result was in contrast to that in *Morse*, where the inventor sought to capture for himself all future developments through a broad method claim describing electromagnetism "however developed." *Id.* at 537-38.

This Court's cases, before and after, are consistent with the approach of *O'Reilly v. Morse* and *The Telephone Cases*. In *Le Roy v. Tatham*, 55 U.S. (14 How.) 156 (1852), the Court held that the practical application of a newly-discovered principle—a certain property of lead that it would form a bond if poured under certain pressure and temperature conditions—could be patented, but only in the form of a specific product or process that was itself new. *Id.* at 175-76. In *Mackay Radio & Tel. Co. v. Radio Corp. of Am.*, 306

U.S. 86, 94 (1939), the Court held, regarding a patent application for a certain type of antennae, that "[w]hile a scientific truth, or the mathematical expression of it, is not patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be." *Id.* at 93. In *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948), the Court held that an inventor claiming a bacterial species that exhibited the property of mutual non-inhibition could not patent the bacteria, as it was merely a claim for a natural phenomenon itself, especially considering that his was not a discovery that applied "the law of nature to a new and useful end." *Id.* at 130. In *Parker v. Flook*, 437 U.S. 584 (1978), the Court disallowed a patent claiming methods for updating alarm limits and held that "if a claim is directed essentially to a method of calculating, using a mathematical formula, even if the solution is for a specific purpose, the claimed method is nonstatutory." *Id.* at 595 (internal quotation marks and citation omitted). In *Gottschalk v. Benson*, 409 U.S. 63 (1972), the Court held that a mere procedure for solving a math problem is not patentable, as it was a method for a general, non-specific, and non-inventive purpose. *Id.* at 67-68. In *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), the Court upheld a human-engineered microorganism as patentable, under 35 U.S.C. § 101, because it was encompassed by the rule of "invention" that "anything under the sun that is made by man" is patentable. *Id.* at 309. Finally, in *Diamond v. Diehr*, 450 U.S. 175 (1981), the Court held that although a mathematical formula embodied in a software program might not qualify for patent protection on its own, application of the formula to perform a new and useful process—in *Diehr*, a process for curing synthetic rubber—did qualify for patent protection. *Id.* at 191-93.

Consistent with these precedents, one of the Federal Circuit's predecessor courts, the Court of Customs and Patent Appeals, attempted to distill this Court's caselaw into a useable guideline for making this ultimately judicial

determination. As the late Judge Rich wrote for that court: "The common thread throughout [this Court's] cases is that [patent] claims which *directly or indirectly preempt* natural laws or phenomena are proscribed, whereas claims which merely *utilize* natural phenomena via explicitly recited manufactures, compositions of matter or processes to accomplish new and useful end results define statutory inventions." *In re Bergy*, 596 F.2d 952, 988 (C.C.P.A. 1979), *vacated as moot*, 444 U.S. 1028 (1980) (emphasis added). There is much to recommend in the *In re Bergy* formulation crafted by Judge Rich—it is wholly on par with this Court's precedents; it is consistent with the other requirements of the Patent Act (such as novelty, *see* 35 U.S.C. § 102, and obviousness, *see* 35 U.S.C. § 103); and it provides a calibrated filter for sorting truly inventive processes from non-inventive efforts to create private exclusionary rights in scientific truths.

C. Applying These Standards, Claim 13 Is Plainly Invalid

As George Ticknor Curtis and Justice Breyer separately recognized over a hundred years apart from one another, the question of patentability where natural laws or phenomena are involved frequently presents weighty and difficult issues. This case does not. Indeed, when one considers the dispositive difference between Morse's unpatentable telegraph claim and Bell's patentable telephone claim, and compares those polestars to claim 13 of the '658 patent, this case becomes an easy one.

As explained above, the dispositive difference of patentability between the Morse and Bell patent claims was that Bell's was limited to the precise apparatus "as herein described"—*i.e.*, the telephone, *The Telephone Cases*, 126 U.S at 531—whereas Morse's sought to claim all uses of electromagnetism "for marking or printing intelligible characters, signs, or letters at any distance," *O'Reilly v. Morse*, 56 U.S. (15 How.) at 112. The Brief for the United

States as *Amicus Curiae*, although urging that the issue required further factual development, acknowledged that claim 13 could not possibly be patentable if—analogous to Morse's patent—it "comprises every substantial practical application of the natural relationship between elevated total homocysteine and deficiencies in the B vitamins." (U.S. Br. at 17) Respondents' Brief in Opposition similarly attempted to cabin this case as more like Bell's than Morse's, urging that "the step of assaying for total homocysteine" was "a further distinct and physical step" that avoided granting Metabolite a "monopoly on a basic scientific step." (Opp. at 9)

But there is no serious argument available that the "assaying" step of claim 13 is itself in any way "inventive." Indeed, although the '658 patent includes extensive claims directed to precise (and, it appears, truly inventive) methods for conducting assays (*e.g.*, claims 1-12), claim 13 requires only "assaying a body fluid for an elevated level of total homocysteine." S.A. 30, column 41, lines 61-62. Comparison with claim 14 confirms the breadth of claim 13—claim 14 is identical in every way to claim 13, except for the additional requirement that the assay be performed "according to the method of claim 7," which itself is ultimately dependent on claim 1—which in turn sets forth a specific five-step method of performing such an assay. S.A. 30, column 42, line 2; *id.*, column 41, lines 34-35; *id.*, column 41, lines 2-19. Claim 13, by contrast, says nothing more than (1) "measure," and (2) "correlate that measurement with a scientific truth"—the relationship between homocysteine levels and cobalamin and folic acid deficiencies.

The analogy to *Morse* is striking. There, Samuel Morse sought exclusionary rights to the use of electromagnetism not in all of its possible applications, but only within the realm of "marking or printing intelligible characters, signs, or letters at any distance." *O'Reilly v. Morse*, 56 U.S. (15 How.) at 112. This further "marking or printing" limitation

did not save his Eighth Claim from a holding of unpatentability, as he was still in effect attempting to claim something that he did not invent. Here, similarly, the named inventors on the '658 patent did not invent the correlation between elevated homocysteine and cobalamin deficiencies; that law of nature existed *a priori*. Nor did those named inventors invent every potential method of "assaying a body fluid"—yet that is exactly what claim 13 seeks to protect.

Claim 14, by contrast, is exactly the same as claim 13, except that it requires the step of "assaying a body fluid" to be performed according to the inventive assaying method set forth in other claims of the '658 patent. That claim, it appears, is much more like the appropriately inventive Fifth Claim of the Alexander Graham Bell Patent, which claimed only the application of electricity converted into sound waves via Bell's claimed apparatus—the telephone. *See The Telephone Cases*, 126 U.S. at 531.

In sum, application of this Court's existing precedent to claim 13 easily yields the conclusion that it contains nothing inventive. Rather, it seeks to claim a private right to exclude all others from utilizing a scientific correlation that the named inventors did not "invent." *See Parker v. Flook*, 437 U.S. at 585, 593 n.15 ("The only novel feature of the method . . . [merely] reveals a relationship that has always existed").

II. SUSTAINING CLAIM 13 OF THE '658 PATENT WOULD HAVE DEVASTATING EFFECTS ON PATIENT HEALTHCARE

If claim 13 of the '658 patent were held by this Court to cover patentable subject matter, it would grant respondents an exclusionary right that would prevent doctors from properly diagnosing and treating cardiovascular disease risk in their patients. And it would surely open the floodgates to a spate of similar patent applications in other areas of medical diagnosis and treatment. These consequences can be avoided by holding that claim 13 of the '658 patent claims nothing inventive.

The AHA has no interest in taking sides in a commercial patent dispute. But it does have a profound interest, consistent with its mission and strategic goal, in ensuring that this particular patent claim is not allowed to interfere with appropriate diagnosis, care, and treatment of cardiovascular health. As noted above, the known relationship among homocysteine levels, increased cardiovascular risk, and vitamin B deficiency allows physicians to screen their patients for risk of heart disease by obtaining homocysteine levels, assessing to see whether elevated homocysteine levels are due to cobalamin or folate deficiency, and then seeking to reduce those increased cardiovascular risks by appropriate treatments, such as prescribing B vitamins and folic acid to mediate those levels. The AHA has issued a Science Advisory addressing homocysteine testing and subsequent treatment. *See* M. René Malinow *et al.*, *Homocyst(e)ine, Diet, and Cardiovascular Diseases: A Statement for Healthcare Professionals From the Nutrition Committee, American Heart Association*, 99 CIRCULATION 178, 178-82 (1999).

A. Homocysteine Testing Is Important For Assessing Patient Risk For Cardiovascular And Other Diseases, And Is Used For Guiding Treatment Of Those Diseases

Homocysteine is a sulphur-containing amino acid that is closely related to the essential amino acid methionine. *See* J. D. Finkelstein, *Homocysteine: A History in Progress*, 58 NUTRITION REVIEWS 193, 193-204 (2000). Methionine is an indispensable protein building block that cannot be produced by the body, must be provided by the diet, and supplies sulfur and other compounds required by the body for normal metabolism and growth. *Id.* Homocysteine is also related to the nonessential protein building block cysteine, which can be made in the human body. *See generally* HOMOCYSTEINE IN HEALTH AND DISEASE (Ralph Carmel & Donald Jacobsen eds., 2001).

An association between elevated homocysteine levels and human disease was first suggested by researchers in the 1960s. *See* J. B. Gibson *et al.*, *Pathological Findings in Homocystinuria*, 17 J. CLIN. PATHOL. 427, 427-37 (1964). At that time, researchers found that high homocysteine concentrations in the blood were associated with premature cardiovascular disease. *Id.* In 1969, homocysteine was affirmatively correlated with the risk of cardiovascular disease and stroke. *See* Kilmer S. McCully, *Vascular Pathology of Homocysteinemia: Implications for the Pathogenisis of Arteriosclerosis*, 56 AM. J. PATHOL. 111, 111-28 (1969). During the last 15 years, it has been repeatedly documented, through epidemiological studies, that even a moderately elevated homocysteine level in blood serum or plasma is a strong and independent risk factor for cardiovascular disease and stroke. *See, e.g.*, Robert Clarke *et al.*, *Hyperhomocysteinemia: An Independent Risk Factor for Vascular Disease*, 324 N. ENGL. J. MED. 1149, 1155 (1991); O. Nygård *et al.*, *Total Homocysteine and Cardiovascular Disease*, 246 J. INTERNAL MED. 425, 425-54 (1999).

Several studies have found that there is a relationship between the blood levels of B vitamins and homocysteine concentrations in the blood. *See, e.g.*, Marianne Verhaar *et al.*, *Folates and Cardiovascular Disease*, 22 ARTERIOSCLER. THROM. VASC. BIOL. 6, 6-13 (2002). Because the B vitamins assist in metabolizing homocysteine, scientists directly assay homocysteine (and other substances) in order to screen for, among other things, cobalamin (vitamin B_{12}) and folate (vitamin B_9) deficiencies. It is believed that the body regulates the homocysteine concentration in the body with the aid of several B vitamins, including folic acid. *Id.* Apart from a genetic predisposition, a shortage of these vitamins can also lead to an increased concentration of homocysteine in the blood. *Id.* However, cobalamin deficiency accounts for only a minority of elevated homocysteine levels; inborn errors of homocysteine metabolism, renal insufficiency, hypothyroidism, alcohol

abuse, enzyme polymorphisms, and other conditions account for the rest.

Cardiovascular Diseases. In the area of cardiovascular diseases, homocysteine testing is used to assess the level of risk for heart attack or stroke. Recent findings indicating graded association of plasma homocysteine levels with cardiovascular risk suggest that the availability of laboratory testing for plasma homocysteine levels can improve the assessment of risk, particularly in patients with a personal or family history of cardiovascular disease. Likewise, homocysteine testing can be ordered as part of a general cardiac-risk assessment, depending on the patient's age and other risk factors. It may also be ordered following a heart attack or stroke to help guide treatment.

Studies have suggested that people who have elevated homocysteine levels have a much greater risk of heart attack or stroke than those with average levels. *See* Verhaar *et al.*, *supra*, at 6-13. "It's pretty clear from most cross-sectional and case-controlled studies and some prospective studies that hyperhomocysteinemia increases the risk for not only myocardial infarction, but also coronary artery disease, peripheral vascular disease, stroke, cerebrovascular disease, restenosis of coronary arteries that have undergone balloon angioplasty, and even death from coronary artery disease." L. Stokes *et al.*, *Blood Levels of Homocysteine and Increased Risk of Cardiovascular Disease*, 160 ARCH. INTERNAL MED. 422, 422-34 (2000). At present, the AHA has not established a direct correlation between homocysteine levels and heart attacks, nor evidence that lowering these levels will with certainty reduce the rate of cardiovascular events, but the AHA does acknowledge strong evidence of a relationship between homocysteine levels and cardiovascular risk. *See* Malinow *et al.*, *supra*, at 178-82.

Since measuring homocysteine levels to determine cardiac risk is a relatively new use for the test, a standardized

interpretation of the measured value has yet to be determined. *Id.* In many people, homocysteine levels can be decreased by taking extra levels of folic acid, vitamin B_{12}, and vitamin B_6—the B-complex vitamins that drive homocysteine metabolism. In others, different results will obtain. Nonetheless, because it may well help (and should not hurt), many doctors and researchers consider folic acid supplementation to be an effective strategy for reducing the quantity of homocysteine in the blood, possibly lessening the risk of cardiovascular and other ailments attributable to homocysteine.

The AHA has a direct interest in the results of ongoing research in this field, and in having its view of the science in this field disseminated throughout the healthcare industry. This is so because a mild to moderate elevation in homocysteine can increase the risk of coronary artery disease by 2.5 times. Projections from a number of small studies suggest that lowering homocysteine by only 5 µmol/L may reduce the death rate from coronary artery disease by 10 percent, C. J. Boushey *et al.*, *A Quantitative Assessment of Plasma Homocysteine As A Risk Factor For Vascular Disease,* 274 J. AM. MED. ASSOC. 1049, 1049-57 (1995), although this has not yet been demonstrated conclusively in large, long-term randomized clinical trials. The volume of homocysteine testing has grown steadily since the early 1990s, when prospective trials and case-controlled studies started showing that this amino acid was associated with an increased risk for cardiovascular disease. Indeed, the record in this case reflects that as these trials and studies became known, and the AHA published its "Science Advisory on Homocysteine, Diet and Cardiovascular Diseases" for physicians, the demand for homocysteine tests "seemed to skyrocket," and petitioner "couldn't keep up with the work" occasioned by all of the physician requests for homocysteine assays. J.A. 168 [Tr. 1423].

Other Diseases. Significantly, elevated homocysteine levels may be indicators of diseases and maladies beyond

cardiovascular disease and stroke. Elevated homocysteine levels have also been associated with adverse pregnancy outcomes, such as spontaneous early abortion and birth defects. *See generally* S. E. Vollset *et al.*, *Plasma Total Homocysteine, Pregnancy Complications, and Adverse Pregnancy Outcomes: The Hordaland Homocysteine Study*, 55 OBSTETRICAL & GYNECOLOGICAL SURVEY 595 (2000). Assaying for B vitamin and folate deficiencies and then supplementing any noticed folate deficiencies with folic acid during the pre-conception period and pregnancy has been shown to substantially decrease the incidence of birth defects, and may reduce the incidence of some pregnancy complications, such as spontaneous abortions. *Id.*

Some studies have also identified an association between elevated homocysteine levels and impaired cognitive performance and dementia, which may portend findings that diseases such as Alzheimer's may be in some ways influenced by homocysteine levels in the body. *See* Sudha Seshadri *et al.*, *Plasma Homocysteine as a Risk Factor for Dementia and Alzheimer's Disease*, 346 N. ENGL. J. MED. 476, 476-83 (2002). Even moderately elevated levels of homocysteine in the body may be associated with an increased risk of developing dementia, or with an increase in the rate of disease progression in those individuals already afflicted. *Id.* While more studies need to be done, reduction of homocysteine levels has been shown to have a positive impact on cognitive performance in elderly individuals with mild cognitive impairment, and to increase regional cerebral blood flow. *Id.*

There is also current research being done on the association between cancer, particularly breast and colon cancers, and impaired homocysteine metabolism. *See* Shumin M. Zhang *et al.*, *Plasma Folate, Vitamin B_6, Vitamin B_{12}, Homocysteine, and Risk of Breast Cancer*, 95 J. NAT. CANCER INST. 373, 373-80 (2003); L. Joseph Su & Lenore Arab, *Nutritional Status of Folate and Colon Cancer Risk: Evidence From NHANES I Epidemiologic Follow-up Study*,

11 ANN. EPIDEMIOLOGY 65, 65-72 (2001). Finally, researchers have also noticed an association between homocysteine levels and depression and other neuropsychiatric disorders. *See* M. Fava *et al.*, *Folate, Vitamin B_{12}, and Homocysteine in Major Depressive Disorder*, 154 AM. J. PSY. 426, 428 (1997). More work remains to be done in these and other areas in order to develop strategies for further assessing these correlations (and suspected connections) between homocysteine and various physical and neuropsychiatric diseases, as well as adopting strategies to improve the healthcare of individuals with elevated homocysteine levels in light of such findings. Even so, physicians are already treating identified vitamin B deficiencies with vitamin supplements with the goal of reducing homocysteine levels and thereby improving overall patient health.

In the AHA's specific area of interest, homocysteine testing is becoming an important tool for assessing cardiovascular risk. Screening of homocysteine levels in the appropriate at-risk patients, followed by prophylactic vitamin supplementation, while still being investigated, is commonly undertaken by physicians to reduce this adverse risk factor.

B. Claim 13 Of The '658 Patent, If Left Standing, Would Prevent Doctors From Following The AHA's Advisory

If upheld, the Federal Circuit's decision would prohibit doctors from following the suggestions in the AHA's Science Advisory in their care of cardiac patients. That would be a profoundly regrettable result for patient care.

As outlined above, there is widespread epidemiological evidence demonstrating a correlation between plasma homocysteine and cardiovascular disease. However, there is at present no definitive study suggesting that reducing homocysteine levels by increasing patient intake of folic acid via diet or vitamin supplement will in fact reduce cardiovascular disease risk. In light of the available data, the

American Heart Association has published a Science Advisory regarding homocysteine testing, with comments as follows.

- Until results of controlled clinical trials become available, population-wide screening is not recommended, and emphasis should be placed on meeting current recommended daily allowances for folate, as well as vitamins B_6 and B_{12}, by intake of vegetables, fruits, legumes, meats, fish, and fortified grains and cereals.
- For patients at a high risk of cardiovascular disease, either through genetic or environmental factors, a strategy may include screening in selected patients (*e.g.*, those with personal or family history of premature cardiovascular disease; those with renal dysfunction or renal failure, malnutrition, hypothyroidism; those taking certain medications; and those with recent nitrous oxide exposure) to uncover fasting plasma homocysteine levels associated with augmented risk status.
- After confirming high homocysteine concentration, it is important to check the vitamin status, owing to the inverse relationships reported between homocysteine and blood levels of folate, B_6, and B_{12}, although it should be recognized that there is currently no firm basis for recommending specific therapeutic targets for homocysteine levels. Measuring the level of plasma methylmalonic acid is the next step in determining vitamin B_{12} deficiency. A useful algorithm for the diagnosis of vitamin deficiency, beyond direct determination of blood levels of this vitamin, is described in DIETARY REFERENCE INTAKES FOR THIAMIN, RIBOFLAVIN, NIACIN, VITAMIN B_6, FOLATE, VITAMIN B_{12}, PANTOTHENIC ACID, BIOTIN, AND CHOLINE (The National Academies Press 1998).

- In high-risk patients, it may also be advisable to increase their intake of vitamin fortified foods and/or to suggest the daily use of supplemental vitamins, *i.e.*, 0.4 mg of folic acid, 2 mg of vitamin B_6, and 6 mg of vitamin B_{12}, with appropriate medical evaluation and monitoring.
- Treatment may include higher doses of those vitamins according to the response of homocysteine. However, such treatment is still considered experimental, pending results from intervention trials showing that homocysteine lowering favorably affects the evolution of arterial occlusive diseases.

See Malinow *et al.*, *supra*, at 178-82.

AHA has a profound concern that, if the Federal Circuit's judgment is not reversed, physicians will not legally be able to follow the AHA Advisory set forth above. AHA encourages physicians who order homocysteine assays to then "correlate" those results to determine patient risk and the appropriate course of treatment. Given the scope of claim 13 as upheld to date by the courts in this case, it is difficult to see how a doctor could prescribe vitamin therapy to lower a patient's elevated homocysteine level without also making the correlation that infringes that patent claim. Indeed, it is difficult to see how a doctor could examine a patient's elevated homocysteine level and merely *consider* the possibility that the elevated level was due to cobalamin deficiency (a relationship the doctor would have learned in medical school) without similarly infringing claim 13.

But the adverse effect of the courts' decisions in this case are obviously not limited to cardiac care. In view of the several other correlations between homocysteine levels and other conditions, diseases, and maladies, in areas such as cancer, pregnancy, neuropsychiatric disorders, and dementia, claim 13 of the '658 patent creates the very real potential for private capture of every possible manner and use of measuring homocysteine levels in human beings. Such a

result could have tragic consequences indeed for the health of our Nation's citizens.

C. Reversing The Judgment Of The Federal Circuit Will Correctly Balance The Appropriate Rewards Of The Patent System With The Needs For Proper Patient Care

There can be no doubt that a properly calibrated patent system creates positive incentives for the development of new and useful pharmaceuticals, medical devices, and diagnostic and treatment methods, all to the benefit of public health and safety. *See, e.g., Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 63-64 (1998). But when, as here, a purported "inventor" is allowed to claim exclusionary rights over something that is truly noninventive, but instead is an *a priori* scientific truth, the "carefully crafted bargain" of the patent system, *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 151 (1989), is distorted beyond both congressional intent and its constitutional moorings.

It is important that this Court maintain this proper balance. The simple two-step "measure, then correlate" process set forth in claim 13 of the '658 patent, which requires only an assay done by any method under the sun, followed by "a simple conclusion that a cobalamin/folate deficiency exists" (Pet. App. 18a), is, under no reasonable understanding of the word, an "invention." Yet many of the other claims of the '658 patent, including claim 14, appear to set forth true novel and useful "inventions"—specific new methods for performing assays that merely utilize the scientific truth—within the meaning of the Constitution and the Patent Laws. That line—between claim 13 and claim 14—is indicative of the careful balance in the patent system that this Court's decision should maintain.

The importance of maintaining this balance cannot be overstated. In the three decades following the 1950s, very few medical-procedure patents were issued. *See, e.g.,*

Edward Felsenthal, *Medical Patents Trigger Debate Among Doctors*, WALL ST. J., Aug. 11, 1994, at B1, B6. More recently, patent attorneys have estimated that the Patent and Trademark Office (PTO) grants at least a dozen medical procedure patents each week. Brian McCormick, *Just Reward or Just Plain Wrong? Specter of Royalties from Method Patents Stirs Debate*, AM. MED. NEWS, Sept. 5, 1994, at 3, 3. And our very simple search of an electronic database of U.S. patents conducted shortly before filing this brief disclosed over 300 patents containing method claims that include steps of "assaying" and "correlating."

Obviously, many, if not most or all of these 300-plus patents set forth actual inventions and merely utilize the scientific truths as a component of the invention (in the same way that *amicus* believes that claim 14 of the '658 patent sets forth an actual, patentable invention). But this Court's careful guidance is needed to ensure that the PTO is not, after the Court's decision in this case, inundated with patent claims similar to claim 13 that claim nothing more than assays plus correlations of those assay results with immutable scientific truths. That would have disturbing consequences for the patent system, for medical diagnoses, and for patient health care. The Court should maintain the proper balances in these areas by reversing the judgment of the Federal Circuit and holding that claim 13 of the '658 patent claims no "invention" within the meaning of the Constitution and the Patent Act.

CONCLUSION

For these reasons, *amicus* respectfully urges the Court to reverse the decision below.

Respectfully submitted,

DAVID WM. LIVINGSTON
EXECUTIVE VICE PRESIDENT
CORPORATE SECRETARY &
GENERAL COUNSEL
AMERICAN HEART ASSOCIATION
7272 Greenville Avenue
Dallas, Texas 75231-4596
(214) 706-1246

GREGORY A. CASTANIAS
(Counsel of Record)
51 Louisiana Avenue, N.W.
Washington, D.C. 20001-2113
(202) 879-3939

Counsel for Amicus Curiae

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No. 04-607

IN THE

Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS, dba LABCORP.

Petitioner,

v.

METABOLITE LABORATORIES, INC., *et al.*,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

AMICUS CURIAE BRIEF OF AMERICAN INTELLECTUAL PROPERTY LAW ASSOCIATION IN SUPPORT OF RESPONDENT

MELVIN C. GARNER
President
AMERICAN INTELLECTUAL PROPERTY LAW ASSOCIATION
2001 Jefferson Davis Highway
Suite 203
Arlington, VA 22202
(703) 415-0780

DENISE M. KETTELBERGER
Counsel of Record
REBECCA A. BORTOLOTTI
HEMA L. VISWANATHAN
Merchant & Gould PC
3200 IDS Center
80 South Eighth Street
Minneapolis, MN 55402
(612) 332-5300

Counsel for Amicus Curiae

199308

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AMICUS CURIAE BRIEF OF THE AMERICAN INTELLECTUAL PROPERTY LAW ASSOCIATION IN SUPPORT OF RESPONDENT

The American Intellectual Property Law Association ("AIPLA") respectfully submits this Brief as *amicus curiae* in support of Metabolite Laboratories. AIPLA urges the Court to leave unchanged the current test described in *Diamond v. Diehr*, 450 U.S. 175 (1981), for evaluating patentable subject matter under 35 U.S.C. § 101. The *Diehr* test properly reflects Congress's intent that "anything under the sun made by man" is patentable subject matter.

STATEMENT OF INTEREST[1]

AIPLA has no interest in any party to this litigation or stake in the outcome of this case, other than its interest in seeking a correct and consistent interpretation of the law affecting intellectual property.

AIPLA is a voluntary bar association of more than 17,000 members who work with patents, trademarks, copyrights, trade secrets, and the legal issues that intellectual property presents. AIPLA's members include attorneys in private and corporate practice and in government service who secure, license, enforce, and defend against infringement of intellectual property rights.

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1. In accordance with Supreme Court Rule 37.6, AIPLA states that this brief was not authored, in whole or in part, by counsel to a party, and that no monetary contribution to the preparation or submission of this brief was made by any person or entity other than AIPLA or its counsel.

AIPLA sought consent to file this *amicus curiae* brief from the counsel of record for all parties, pursuant to Supreme Court Rule 37.3(a). Counsel for all parties have consented. Copies of the letters of consent have been filed concurrently with this Brief.

QUESTION PRESENTED

The Petitioner's question has the potential to implicate several aspects of patent law, most notably, issues arising under 35 U.S.C. § 112. In addition, the question raises alleged public policy concerns over limiting a physician's practice of medicine.

This Court elected to consider the following question: "whether a method patent setting forth an indefinite, undescribed, and non-enabling step directing a party simply to 'correlat[e]' test results can validly claim a monopoly over a basic scientific relationship used in medical treatment such that any doctor necessarily infringes the patent merely by thinking about the relationship after looking at a test result."

This question does not clearly articulate recognized patent law issues. However, the terminology used in the question presents the issue of whether Claim 13 of U.S. Patent No. 4,940,658 ("the '658 patent") satisfies the definiteness, written description, and enablement requirements of 35 U.S.C. § 112. Claim 13 was found by the jury to meet these requirements, the trial court held substantial evidence existed to support the jury's verdict,[2] and the Federal Circuit affirmed.[3]

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2. *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, No. 99-Z-870 (D. Colo. Nov. 19, 2001).

3. *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1372 (Fed. Cir. 2004).

The second part of the Petitioner's Question, improperly focuses on one step of a multistep process claim and invokes the now discredited–"mental steps" and "human steps" doctrines.[4]

The section 112 patentability issues and public policy concerns presented in the Petitioner's Question and initial Petition for Writ of Certiorari do not appear to be the issues under consideration by this Court. Instead, this Court's request for the views of the Solicitor General suggests an intention to consider whether Claim 13 satisfies a different section of the Patent Act, 35 U.S.C. § 101, defining statutory subject matter.[5] Specifically, the Court appears willing to consider whether Claim 13 falls within one of the judicially created exceptions to patentable subject matter: laws of nature, natural phenomena, and abstract ideas, even though this issue was not raised or argued at trial or on appeal to the Federal Circuit.

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4. *See In re Musgrave*, 431 F.2d 882, 893 (C.C.P.A. 1970) (rejecting the mental steps doctrine); *Alco Standard Corp. v. Tennessee Valley Authority*, 808 F.2d 1490, 1496 (Fed. Cir. 1987) (rejecting the human steps doctrine). *See also Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility*, 1300 Off. Gaz. Pat. Office 142 (Nov. 22, 2005) (discussing the rejection of the mental steps and human steps doctrines).

5. On February 28, 2005, this Court requested briefing by the Solicitor General on the following question: "Is the patent invalid because one cannot patent 'laws of nature, natural phenomena, and abstract ideas?'" Brief for the United States as Amicus Curiae at 4, *Lab. Corp. of Am. v. Metabolite Labs., Inc.*, 126 S. Ct. 601 (2005) (No. 04-607) [hereinafter "Brief for the United States"].

The question for review implied by the Court's question to the Solicitor General is whether a practical application of a natural phenomenon is patentable subject matter under the broad standard of 35 U.S.C. § 101.

SUMMARY OF ARGUMENT

Petitioner never alleged at trial that Claim 13 failed to satisfy the requirements of 35 U.S.C. § 101. In addition, the issue was never presented to the Federal Circuit for review and should be considered waived. The record lacks any evidence or analysis of whether Claim 13, as a whole, meets the requirements of section 101. The record is underdeveloped largely because the Parties did not dispute any aspect of the "assaying" step and focused solely on the "correlating" step.[6] Because this Court generally refrains from addressing issues that were not raised or considered below, it should decline to consider, in the first instance, whether Claim 13 recites patentable subject matter.

If the Court nonetheless considers the issue, the case should be remanded to the trial court for an analysis of appropriate facts on the record. As this Court has recognized, Congress broadly defined the scope of patentable subject matter under section 101 to encompass "anything under the sun made by man."[7] The language of section 101 places few limits on the types of invention eligible for patent protection. The broad language of the statute reflects Congress's judgment regarding how best to fulfill its Constitutional

6. *Metabolite*, 370 F.3d at 1364 & n.1.

7. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) (quoting S. Rep. No. 82-1979, at 5 (1952); H.R. Rep. No. 82-1923, at 6 (1952)).

mandate to promote the advancement of the useful arts and sciences.

Consistent with the broad language of section 101, this Court has recognized only a few exceptions to patentable subject matter. These exceptions have been narrowly construed to preclude only those patent claims directed to laws of nature, natural phenomena, or abstract ideas, in isolation.[8] Although laws of nature, natural phenomena, and abstract ideas cannot be patented in isolation, the application of a law of nature, natural phenomena, or abstract idea to a useful process or product may be patentable under section 101.[9] It is irrelevant whether a portion of a patent claim, viewed in isolation, would or would not satisfy section 101. Rather, if the claim as a whole recites patentable subject matter, it satisfies the liberal standard of section 101.[10]

Proper analysis of Claim 13 evaluates if the claim in its entirety, including the preamble and all method steps, is directed to a law of nature, a natural phenomenon, or an abstract idea in isolation, or if the claim instead is directed to the application of a law of nature to a practical purpose. Claim 13 recites a method for diagnosing a deficiency in cobalamin or folate including a preamble calling out a

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8. *Diamond v. Diehr*, 450 U.S. 175, 184 (1981).

9. *See* Edward C. Walterscheid, *Divergent Evolution of the Patent Power and the Copyright Power*, 9 Marq. Intell. Prop. L. Rev. 307, 348 (2005) ("If [natural phenomena, laws of nature, or abstract ideas] are employed . . . as to produce a utilitarian result, the patentable 'discovery' resides in the embodiment or process that makes use of them to produce the useful result . . . .").

10. *Diehr*, 450 U.S. at 192.

diagnostic purpose and steps that accomplish that purpose. On remand, the trial court should consider whether the claim as a whole, including the preamble and the method steps of "assaying" and "correlating," meets the requirements set out in *Diamond v. Diehr*, where this Court construed and applied the constitutional mandate to promote the useful arts and sciences.

As a whole, does Claim 13 describe a useful application of the inventors' discovery that an elevated level of total homocysteine is an indicator of cobalamin or folate deficiency? If a factual basis is established to show that Claim 13 recites more than a mere law of nature in the abstract, the claim should pass the low threshold for patentable subject matter under section 101. Other provisions of the patent laws, including section 112 issues of definiteness, written description, and enablement, as well issues under sections 102 (novelty) and 103 (non-obviousness) can then be employed to test the patentability of the claim.

AIPLA urges the Court not to disturb the broad and accessible threshold of statutory subject matter that has fostered innovation and public disclosure over a wide variety of useful arts, and importantly, in new and emerging fields of technology, including the important area of diagnostic medicine involved in this case.

ARGUMENT

I. THIS CASE IS NOT THE APPROPRIATE VEHICLE FOR ADDRESSING THE SCOPE OF PATENTABLE SUBJECT MATTER UNDER SECTION 101.

This Court generally refrains from addressing issues that were not raised before, or considered by, the lower courts. *See* Sup. Ct. R. 14.1(a); *Adarand Constructors, Inc. v. Mineta*, 534 U.S. 103, 109 (2001); *Taylor v. Freeland & Kronz*, 503 U.S. 638, 646 (1992). As several *amici*, including the Office of the Solicitor General, have indicated, Petitioner never argued to the trial court or to the Federal Circuit that Claim 13 failed to satisfy section 101, and thus waived the issue.

Petitioner's section 101 invalidity claim was never presented to the jury at trial. The special verdict form presented to the jury recited the following for invalidity: lack of enablement, insufficient written description, indefiniteness, obviousness, and anticipation. Enablement, written description, and indefiniteness are all invalidity defenses arising under 35 U.S.C. § 112. Obviousness is a defense under section 103, and anticipation arises under section 102. None of Petitioner's invalidity defenses presented at trial involved section 101.

Consistent with its trial presentation, Petitioner's Brief to the Federal Circuit never mentioned section 101, nor did it contain any argument that Claim 13 failed to recite patentable subject matter. Rather, Petitioner simply made a single passing reference to this Court's decision in *Diehr*, in support of Petitioner's argument that the Federal Circuit should reverse the district court's claim construction.

The Federal Circuit was never presented with argument relating to the assaying step of the multistep claim. The parties rested the infringement analysis and issues of claim construction on the correlating step of Claim 13. In response, the Federal Circuit noted "[t]his Court, therefore, does not address the assaying step." *Metabolite*, 370 F.3d at 1364. Because the failure to meet the requirements of section 101 was never raised below, it is not surprising that the Federal Circuit's opinion did not address this issue.

This Court should not address, in the first instance, an issue that was never presented to the district court or to the Federal Circuit. This case is not of such exceptional importance that it warrants review on an issue neither presented, nor passed upon, below. *Cf. Duignan v. United States*, 274 U.S. 195, 200 (1927). AIPLA submits the Court should, at most, remand the case for development of the record on Petitioner's section 101 invalidity claim so that the trial court and/or the Federal Circuit can meaningfully review the issue, *if it is to be* considered *by this Court*.

II. *DIAMOND v. DIEHR* CARRIES OUT THE INTENT OF CONGRESS TO BROADLY DEFINE THE SCOPE OF PATENTABLE SUBJECT MATTER

The United States Constitution authorizes Congress "[t]o promote the Progress of . . . useful Arts, by securing for limited Times to . . . Inventors the exclusive Right to their . . . Discoveries." U.S. Const. art. I, § 8, cl. 8. In pursuit of its Constitutional mandate to promote the progress of the useful arts, Congress broadly defined the scope of patentable inventions in 35 U.S.C. § 101, which states:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of

> matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of [Title 35 of the United States Code].[11]

This Court has interpreted the language of section 101 broadly: "In choosing such expansive terms as 'manufacture' and 'composition of matter,' modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope." *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980). Devoid of limiting language, section 101 readily accommodates the rapid pace of innovation and the assimilation of new technologies, including technologies never anticipated at the time section 101 was enacted. Since 1796, the broad and expansive terms of the Patent Act have embraced inventions in fields as diverse as mechanical, electrical, and chemical subject matter, electronics, plants, animals, biotechnology, nanotechnology, computers, and software.

As this Court recognizes, the legislative history of the 1952 Patent Act shows that Congress intended inventors to be able to patent "anything under the sun that is made by man." *Chakrabarty*, 447 U.S. at 308-09 (quoting S. Rep. No. 82-1979, at 5 (1952); H.R. Rep. No. 82-1923, at 6 (1952)).

One strength of the Patent Act has been its lack of specific exclusionary limitations; permitting broad discretion in judicial interpretation and leaving the door open for as yet uncontemplated innovations and technologies. *See, e.g.*, Robert Greene Sterne & Lawrence B. Bugaisky, *The Expansion of Statutory Subject Matter Under the 1952 Patent*

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11. 35 U.S.C. § 101 (2000).

Act, 37 Akron L. Rev. 217, 225 (2004) ("Based on [the] history, there appears to be no compelling reason why future patentable subject matter in any technology area cannot be addressed under the current statutory provision."). Limiting access to the U.S. patent system by excluding technological advances such as the one at issue in this case, would stifle disclosure of inventions, limit research and development, and negatively impact innovations, particularly in emerging technologies.

Congress intentionally set the threshold for patentable subject matter under section 101 to be low. Recognizing this intent, the Court has defined exceptions narrowly so as to allow for a broad expanse of patentable subject matter. As the first hurdle to patentability, a broad scope of eligible subject matter permits easy entry for new and emerging types of subject matter. The public need not be concerned about this low threshold, however, as proof of patentability requires more than merely satisfying the subject matter requirements of section 101. The public domain is well protected by other, more stringent, criteria for patentability under Title 35, including novelty, nonobviousness, and sufficient disclosure. The doctrine of inherent anticipation prevents a patent claim from reciting solely a preexisting phenomenon, known or unknown, such as a principle of nature.

This Court's decision in *Diamond v. Diehr* presents a well-accepted and useful test for analyzing patentable subject matter under section 101. Although laws of nature, natural phenomena, and abstract ideas are, *in isolation*, unpatentable, this Court distinguished unpatentable abstract ideas from the practical and therefore patentable *application* of such discoveries. "It is now commonplace that an *application* of a law of nature or mathematical formula to a known structure

or process may well be deserving of patent protection." *Diehr*, 450 U.S. at 187 (emphasis added); *see also Parker v. Flook*, 437 U.S. 584, 590 (1978) ("[I]t is equally clear that a process is not unpatentable simply because it contains a law of nature or a mathematical algorithm."); *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948).

In *Diehr*, this Court held that a claim that incorporated a mathematical equation constituted patentable subject matter because the claim, as a whole, defined a rubber molding process and not just an equation. *Diehr*, 450 U.S. at 192–93. Distinguishing *Parker v. Flook* as merely reciting a mathematical formula, the Court stated: "In contrast [to *Flook*], the respondents here do not seek to patent a mathematical formula. Instead, they seek patent protection for a process of curing synthetic rubber." *Diehr*, 450 U.S. at 187.

The mathematical formula at issue in *Diehr* was well known, as were the process steps of installing rubber in a press, closing the mold, and determining the temperature of the mold. Additional steps included "constantly recalculating the appropriate cure time through the use of the formula and a digital computer, and automatically opening the press at the proper time." Citing *Parker v. Flook*, the Court noted that "insignificant post-solution activity will not transform an unpatentable principle into a patentable process." *Id.* at 193. This was not the case for the *Diehr* claims, which applied the formula to a useful process:

> On the other hand, when a claim containing a mathematical formula implements or applies that formula in a structure or process which, when considered as a whole, is performing a function

> which the patent laws were designed to protect (*e.g.*, transforming or reducing an article to a different state or thing), then the claim satisfies the requirements of §101.

Id.

Flook was further distinguished in *Diehr* because the patent application in *Flook* lacked sufficient details of use outside the mathematical formula:

> We were careful to note in *Flook* that the patent application did not purport to explain how the variables used in the formula were to be selected, nor did the application contain any disclosure relating to chemical processes at work or the means of setting off an alarm or adjusting the alarm limit. All the application provided was a 'formula for computing an updated alarm limit.'

Id. at 187 (citations omitted).

The *Diehr* Court explained that although laws of nature, natural phenomena, and abstract ideas are not patentable in isolation, if the claim as a whole recites an application of a mathematical formula to a new and useful process, section 101 is satisfied. *Id.* By the same token, the *Diehr* Court said that the unpatentability of a mathematical formula cannot be circumvented by limiting the use of the formula to a particular technological environment or by insignificant post-solution activity. "To hold otherwise would allow a competent draftsman to evade the recognized limitations on the type of subject matter eligible for patent prosecution." *Id.*

Applying the *Diehr* test for patentable subject matter under section 101, a first inquiry asks: does the claim include a mathematical formula, scientific principle, or phenomenon of nature? If so, does the claim, as a whole, apply or implement the mathematical formula, scientific principle, or phenomenon of nature in a useful process or product? If the answer is yes, the claim satisfies section 101.[12]

The *Diehr* test as developed by the Federal Circuit provides ample opportunity to determine if the application of a claimed invention would "wholly preempt" a natural principle. The scope of a patent claim is determined by considering not only the claim terms themselves, but also the meaning to be given those terms in light of the patent specification and the prosecution history, and in the eyes of a person of skill in the art. Moreover, a patent's preamble language (in this case, "[a] method for detecting a deficiency of cobalamin or folate in warm-blooded animals") may also provide definition of a useful purpose that reflects an accepted category of patentable subject matter within the terms of section 101.

The Federal Circuit has followed this Court's *Diehr* decision in analyzing patentable subject matter under section 101. *State Street Bank & Trust Co. v. Signature Fin. Group, Inc.*, 149 F.3d 1368, 1373-74 (Fed. Cir. 1998); *In re Alappat*, 33 F.3d 1526, 1544 (Fed. Cir. 1994); *Arrhythmia Res. Tech., Inc. v. Corazonix Corp.*, 958 F.2d 1053, 1057 (Fed. Cir. 1992) ("[C]laims to a specific process or apparatus that is

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12. In *Diehr*, the Court also noted that a claim may be directed to patentable subject matter regardless of whether it would satisfy the novelty requirement of section 102, or the nonobviousness requirement of section 103. *Diehr*, 450 U.S. at 189-91.

implemented in accordance with a mathematical algorithm will generally satisfy section 101.").[13]

The Federal Circuit defined the threshold inquiry for any section 101 analysis as whether the invention as a whole is directed to patentable subject matter. *State Street Bank*, 149 F.3d at 1374. The focus of the inquiry is on the essential characteristics of the subject matter as a whole, namely its practical utility. *Id.* In *State Street Bank*, a determination that an algorithm in a patent claim was practically applied as a step in the method claim was sufficient for the claim to meet the requirements of section 101.

Where *State Street Bank* examined the patentable subject matter criteria for a machine that transforms data, the Federal Circuit thereafter applied the same criteria to process patent claims in *AT&T v. Excel Communications, Inc.*, 175 F.3d 1352 (Fed. Cir. 1999). Although *Diehr* held section 101 could be satisfied by a claimed invention that "transforms" an article to a different state, the Federal Circuit in *AT&T* explained that physical transformation is not an exclusive requirement, but rather an example of one way that a mathematical algorithm in a claimed process can be limited to a practical application, namely by producing a useful, concrete, tangible result. *Id.*

A process can produce a useful, concrete, tangible result, even when one of the steps could be carried out mentally. The Federal Circuit (and its predecessor court) have expressly rejected the "mental steps" and "human steps" doctrines, with

13. In *Arrhythmia*, Judge Rader noted that this Court's decision in *Diehr* "cut the Gordian knot" of confusing precedent that unnecessarily restricted the scope of patentable subject matter under section 101. *Arrhythmia*, 958 F.2d at 1061 (Rader, J., concurring).

respect to patentable subject matter. The Court of Customs and Patent Appeals noted that the fact that some process steps were carried out in the human mind did not render a process non-statutory subject matter. *In re Musgrave*, 431 F.2d 882, 893 (C.C.P.A. 1970). Similarly, in *Alco Standard Corp. v. Tennessee Valley Authority*, the Federal Circuit specifically rejected the notion that merely because a human can carry out some or all the steps of a process, the process is unpatentable. 808 F.2d 1490, 1496 (Fed. Cir. 1987). Rather, the practical application test of *State Street* should be applied, in accordance with current law. In sum, the inquiry for purposes of determining statutory subject matter is whether the claimed invention produces a useful, concrete, and tangible result. *Alco Standard*, 808 F.2d at 1496.

The precedents of this Court and the Federal Circuit on patentable subject matter are also reflected in the most recent Guidelines on patentable subject matter published by the United States Patent & Trademark Office. *Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility*, 1300 Off. Gaz. Pat. Office 142 (Nov. 22, 2005). The Guidelines note that a claim contains patentable subject matter if, when taken as a whole, it accomplishes a practical application. The practical application requirement is met if the claimed invention produces a "useful, concrete, and tangible result." *Id.* (citing *State Street Bank*, 149 F.3d at 1375). Although these Guidelines are not controlling, they demonstrate that the Patent Office also follows this Court's *Diehr* analysis when evaluating patentable subject matter under section 101.

In sum, where a claim includes a law of nature, natural phenomenon, or abstract idea (for example, a mathematical algorithm), an accepted analysis for determining the existence

of patentable subject matter under section 101 was announced by this Court in *Diehr*. The *Diehr* test, as applied by the Federal Circuit and utilized by the U.S. Patent Office, focuses on whether the claimed invention as a whole is directed to a practical application of a law of nature, natural phenomenon, or abstract idea to a process or apparatus in a way that produces a useful, concrete, and tangible result. This Court should reaffirm this test for patentable subject matter under section 101.

III. ANALYSIS OF CLAIM 13 FOR PATENTABLE SUBJECT MATTER UNDER SECTION 101 SHOULD APPLY THE *DIEHR* TEST.

Neither the district court nor the Federal Circuit addressed whether Claim 13 recited patentable subject matter. As discussed above, reconsideration of the important issue of patentable subject matter eligibility in a case where the record is not factually developed for the issue does not bode well for the many types of patent claims that might be affected by any such decision.

The Solicitor General and other *amici* suggest that this case be remanded for factual findings consistent with the analysis of patentable subject matter under section 101. An analysis of Claim 13 under section 101 should apply this Court's *Diehr* analysis, on factual evidence developed at trial. Evaluation of patentability under section 101 requires review of the claim as a whole, including the preamble and both method steps, and not merely the *assaying* step or the *correlating* step in isolation.[14]

14. *See Diehr*, 450 U.S. at 192; *State Street Bank*, 149 F.3d at 1375 ("It is irrelevant that a claim may contain, as part of a whole, subject matter which would not be patentable by itself.").

Following the *Diehr* test, a first inquiry might be whether the claimed invention includes a law of nature, natural phenomenon, or abstract idea. Assuming such an exception is found, the claim would then be reviewed as a whole to determine if more than a law of nature, a natural phenomenon, or an abstract idea, is recited. In other words, the proper inquiry for an analysis under section 101 is: Does the claim apply a law of nature, natural phenomenon, or abstract idea to an otherwise acceptable category of patentable subject matter, in a way that produces a useful, concrete, and tangible result?

Claim 13 recites:

> A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> > *assaying* a body fluid for an elevated level of total homocysteine; and
> >
> > *correlating* an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

The preamble of Claim 13 recites that the claim is directed to a diagnostic method for detecting a deficiency of cobalamin or folate in warm-blooded animals. The method steps that follow the preamble recite the actions taken to accomplish the recited diagnostic method: *assaying* a body fluid to determine the amount of total homocysteine in the sample to determine if the amount is elevated; and *correlating* an elevated amount with a diagnosis of cobalamin or folate deficiency.

The '658 patent specification is generally directed to the accurate and early diagnosis of cobalamin and folate deficiencies that can lead to life-threatening disorders. The patent describes prior unsuccessful attempts to find a biological indicator for a deficiency of cobalamin or folate. None of the prior methods measured total homocysteine levels. Recognizing that elevated levels of total homocysteine can be correlated with both cobalamin and folic acid deficiencies, the patentee created the useful diagnostic method that is reflected in Claim 13.[15]

Like the patent claim at issue in *Diehr*, once the claim terms are fully construed and the section 101 issue is considered by the trial court, Claim 13 may be interpreted to include one of the judicially noted exceptions to patentable subject matter: a law of nature, natural phenomenon, or abstract idea (e.g., mathematical algorithm). The claim at issue in *Diehr* included a known mathematical formula that was applied in a process for molding rubber. Claim 13 at issue in this case does not recite a mathematical formula, but in one method step recites "correlating an elevated level of total homocysteine" in a body fluid with a deficiency of cobalamin or folate.

If the newly discovered relationship between total homocysteine and the recited vitamin deficiency is a "law of nature" or "natural phenomenon," the Court should then consider if the law of nature is applied to a practical result, as is proper, or if it is merely claimed in the abstract, which is not proper.

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15. The Federal Circuit noted that no additional confirmatory steps were necessary, and the correlation between total homocysteine levels and vitamin deficiency was novel. *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1361-62 (Fed. Cir. 2004).

The Petitioner dissects Claim 13 into its pieces, choosing to ignore the "assaying" step as lacking novelty, and treating the balance of the claim as non-statutory. Such dissection of the claim is an improper analysis, as the majority in *Diehr* found:

> In order for the dissent to reach its conclusion it is necessary for it to read out of respondents' patent application all the steps in the claimed process which it determined were not novel or "inventive." That is not the purpose of the §101 inquiry and conflicts with the proposition recited above that a claimed invention may be entitled to patent protection even though some or all of its elements are not "novel."

Id. at 194.

In *Diehr*, this Court approached the analysis of the patentable subject matter by comparing the type of subject matter recited in the claims with the statutory categories: "[W]e think that a physical and chemical process for molding precision synthetic rubber products falls within the §101 categories of possibly patentable subject matter." *Id.* at 185. Here the claim is directed to a diagnostic method for detecting a vitamin deficiency.

The claims in *Diehr* involved the "transformation of an article, raw, uncured synthetic rubber, into a different state or thing." The method steps detailed this transformation from loading the mold with the raw material to opening the press at the end of the cure period. "Industrial processes such as this are the types which have historically been eligible to receive the protection of our patent laws." *Id.* However, as

indicated in *State Street Bank*, if a process converts information into a useful, tangible, and concrete result, a statutory process is also created.

As in *Diehr*, analysis of Claim 13 should consider if the claim as a whole contains the type of subject matter that has been eligible to receive the protection of the U.S. patent laws. Claim 13 recites a diagnostic method. The preamble recites the deficiency to be diagnosed, and the method steps describe how the diagnosis is to be accomplished. The format of the claim follows a standard pattern of diagnostic method claims having the diagnostic purpose in the preamble, with steps reciting the analysis of a disease marker and the use of the results of the analysis to determine the diagnosis of disease.

The Court in *Diehr* determined the claim at issue was not directed solely to claiming a mathematical formula, but rather the claimed process employed a well-known mathematical equation. The patent claims did not seek to preempt the use of that equation, but rather sought to "foreclose from others the use of that equation in conjunction with all the other steps in their claimed process." *Id.* at 188.

Similarly, analysis of Claim 13 should examine if the claims as a whole preempt the use of any "law of nature." The Solicitor General's *amicus* brief suggests that Claim 13 *may* run afoul of the rule against claiming every "substantial practical application" of a law of nature, such that the practical effect would be the grant of a monopoly on the law of nature itself.[16] *Gottschalk v. Benson*, 409 U.S. 63, 71-72 (1972).

16. The Solicitor General acknowledges that the record is not fully developed, and thus cannot support a review of the validity of Claim 13 under section 101. *See* Brief for the United States at 17.

Claim 13 recites a method that employs the discovered relationship between a measured amount of total homocysteine in a sample and cobalamin or folate deficiency for purposes of a specific diagnosis. As the Solicitor General acknowledges, it is not clear if the factual record might be developed to expose other potential uses of the discovered relationship outside the claimed diagnosis. In any event, the scope of Claim 13 may not extend beyond the specific diagnostic method recited in the claim.

Applying the *Diehr* test of patentability to Claim 13, a trial court would first consider if the claim recites a basic scientific principle or phenomenon of nature. If so, the court, considering the subject matter of the claim as a whole, including the diagnostic purpose recited in the preamble, and the assaying and correlating steps that carry out the diagnostic method, would determine if the law of nature is applied to a practical method protectable by the U.S. patent laws.

Many existing U.S. patent claims recite diagnostic methods that apply similar relationships between discovered biomarkers and the presence or absence of disease, and will be affected by any changes in the broad scope of patentable subject matter currently granted to medical diagnostic claims. For example, U.S. Patent No. 6,051,379 includes a claim directed to a well-known diagnostic method for detecting a predisposition to breast cancer by analyzing a patient sample for a mutated gene, BRCA-1, and correlating the presence of the mutation with a predisposition to breast cancer. A similar diagnostic method is claimed in U.S. Patent No. 5,599,677, where a measurement of the amount of free prostate-specific antigen (PSA) in a patient sample is correlated to the existence of prostate cancer.

The rapid discovery of biomarkers for disease, elucidation of genetic profiles for subgrouping diseases and patient populations, as well as prediction of an individual's response to therapy, is launching a new era of personalized medicine that will rely heavily on patent exclusivity for the financial stability and incentive to stimulate commercialization of new diagnostic tools.

Patented methods in other technological fields will also be affected by a decision in this case. Such claims could be directed to predicting weather conditions, such as earthquakes, hurricanes, or tornados. For example, U.S. Patent No. 5,546,800 includes a claim that recites the steps of measuring negative ion flow intensity in the air and correlating negative ion flow with imminent tornado formation.

As these examples show, many useful patented inventions apply a natural phenomenon or law of nature to a useful result. Congress intended that inventors of such processes would be able to seek protection via the patent system. Accordingly, AIPLA urges the Court to uphold the broad scope of patentable subject matter that Congress intended for 35 U.S.C. § 101, so that the U.S. patent system will continue to successfully promote the progress of the useful arts.

CONCLUSION

Because the instant case does not properly present the issue of whether Claim 13 contains patentable subject matter under 35 U.S.C. § 101, the Court should not address that issue. At most, the Court should remand for further development of the record and analysis of the 101 issue in the first instance by the trial court.

Should this Court choose to decide the section 101 issue on the limited record available, AIPLA urges the Court not to disturb the broad and accessible threshold of statutory subject matter that has fostered innovation and public disclosure over a wide variety of useful arts, and importantly, in new and emerging technology fields, including the important area of diagnostic medicine involved in this case.

Respectfully submitted,

MELVIN C. GARNER
President
AMERICAN INTELLECTUAL
PROPERTY LAW ASSOCIATION
2001 Jefferson Davis Highway
Suite 203
Arlington, VA 22202
(703) 415-0780

DENISE M. KETTELBERGER
Counsel of Record
REBECCA A. BORTOLOTTI
HEMA L. VISWANATHAN
MERCHANT & GOULD PC
3200 IDS Center
80 South Eighth Street
Minneapolis, MN 55402
(612) 332-5300

Counsel for Amicus Curiae

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Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS (DOING BUSINESS AS LABCORP),

Petitioner,

v.

METABOLITE LABORATORIES, INC. AND COMPETITIVE TECHNOLOGIES INC.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF FOR THE AMERICAN MEDICAL ASSOCIATION, THE AMERICAN COLLEGE OF MEDICAL GENETICS, THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS, THE ASSOCIATION FOR MOLECULAR PATHOLOGY, THE ASSOCIATION OF AMERICAN MEDICAL COLLEGES, AND THE COLLEGE OF AMERICAN PATHOLOGISTS AS *AMICI CURIAE* IN SUPPORT OF PETITIONER

JACK R. BIERIG*
LYNN D. FLEISHER
SIDLEY AUSTIN BROWN & WOOD LLP
One South Dearborn Street
Chicago, IL 60603
(312) 853-7000

Counsel for Amici Curiae

* Counsel of Record

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QUESTION PRESENTED

Whether a method patent setting forth an indefinite, undescribed, and non-enabling step directing a party simply to "correlat[e]" test results can validly claim a monopoly over a basic scientific relationship used in medical treatment such that any doctor necessarily infringes the patent merely by thinking about the relationship after looking at a test result.

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INTRODUCTION AND INTEREST OF *AMICI CURIAE*[1]

Since the time of Hippocrates, a basic tenet of medical ethics has been that discoveries and advances in medical care should be freely shared and openly disseminated. This ethical principle has served to make such discoveries readily available, at minimal cost, for use in the diagnosis and treatment of patients. It also has helped physicians fulfill their fundamental obligation to act in their patients' best interests.

For more than 200 years, the patent laws have, with few exceptions, existed in harmony with the professional ethical duty to publish and disseminate medical advances. Misapplication of the patent laws by the lower courts in this case, however, has created tension with basic principles of medical ethics. This would not have occured if the patent laws had been construed consistently with this Court's precedent.

Specifically, the Federal Circuit has held that Claim 13 of the patent at issue in this case gives the patentees exclusive private ownership not of a new drug, or of a new diagnostic test, or even of a new method of diagnosing a particular disease – but rather of a scientific fact. Claim 13 covers any "correlation," construed by the lower court as merely an "association" or "conclusion" in a physician's mind, between (a) a test result – however obtained – for blood levels of homocysteine and (b) a vitamin deficiency. Claim 13 is thus infringed whenever a physician, having ordered a test (patented or not), reviews the test results with the relationship between homocysteine and vitamin deficiency in mind.

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[1] Pursuant to Rule 37.6, *amici* state that no counsel for any party drafted this brief in whole or in part, and no persons or entities other than *amici* made any monetary contribution to its preparation or submission. Letters of consent have been filed with the Clerk.

The scope of patentable subject matter as established by Congress in the Patent and Trademark Act ("the Act"), although quite broad, does not extend to a physician's consideration of a scientific fact. A patient's elevated levels of the amino acid homocysteine may well indicate a vitamin deficiency. That a physician thinks of that relationship when reviewing laboratory test results, however, is not evidence that the physician is engaging in a "process," as that term is used in Section 101 of the Act, 35 U.S.C. § 101. Rather, it is evidence only that a physician is aware of a pre-existing scientific relationship.

Once recognized, the relationship between elevated homocysteine levels and a potential vitamin deficiency cannot be ignored. Such a fact should be used in the diagnosis and treatment of patients and publicized in order to advance medical science. Properly construed, Section 101 of the Act does not interfere with the spread and use of such information, because allowing a physician to think about the relationship between a test result and a patient's physical condition is not a patentable "process" within the meaning of Section 101.

Of course, if the basic fact that certain test results correlate with a given physical condition were to be incorporated into some useful application, then that application might be a patentable advance over prior art. But the fact of the correlation alone is not, under Section 101, subject matter eligible for patent protection. It therefore cannot, in itself, provide a valid basis for enjoining a laboratory from performing tests – or for discouraging laboratories from providing physicians with information about the significance of test results that physicians can then use in the diagnosis and treatment of patients.

The Federal Circuit's construction of Claim 13 contravenes limitations on the scope of patentable subject matter that have existed for more than two centuries. If affirmed, it will permit patentees to restrict access to, and use of, basic scientific

principles. Allowing a private party to enforce a patent on a scientific fact prevents physicians from exercising their best medical judgment in treating their patients and thereby inhibits the sound practice of medicine. On behalf of their hundreds of thousands of members nationwide, the medical associations that are submitting this brief urge the Court to enforce the limitations imposed by the Act on the subject matter of patents.

The American Medical Association (AMA) is a private, voluntary non-profit organization of physicians and medical students with approximately 250,000 members, who practice in all states and in all fields of medical specialization.[2] The AMA was founded in 1847 to promote the science and betterment of public health. From its inception, the AMA has maintained a Code of Medical Ethics, including a set of core Principles and a Code and Opinions applying those Principles, which guide the ethical practice of medicine. Several of these principles and opinions, as well as reports of the AMA's Council on Ethical and Judicial Affairs, address ethical issues raised by the issuance of patents on medically useful information.[3]

The American College of Medical Genetics (ACMG) is a private, non-profit, voluntary organization of clinical and laboratory geneticists. The Fellows of the ACMG are doctoral level medical geneticists and other physicians involved in the practice of medical genetics. The 1,300 members of the ACMG practice in all states. The ACMG promotes the development and implementation of methods to

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[2] The AMA submits this brief on its own behalf and as a representative of the Litigation Center of the American Medical Association and the State Medical Societies. The Litigation Center is a coalition of the AMA and the medical societies of every state and of the District of Columbia, formed to represent the views of organized medicine in the courts.

[3] *See, e.g.*, Am. Med. Ass'n, *Patenting of Medical Procedures*, 53 Food & Drug L.J. 341 (1998).

diagnose, treat and prevent genetic disease. In order to fulfill this mission, the ACMG strives to 1) advance the art and science of medical genetics by maintaining high standards in education, practice and research; 2) increase access to medical genetic services and improve public health; 3) develop clinical practice guidelines; and 4) establish uniform laboratory standards, quality assurance and proficiency testing. The position of the ACMG is that naturally occurring substances should not, in and of themselves, be patentable.

The American College of Obstetricians and Gynecologists (ACOG) is a non-profit educational and professional organization founded in 1951. With more than 45,000 members in the United States, ACOG is the leading professional association of physicians who specialize in the health care of women. ACOG was established to foster and stimulate improvements in all aspects of the health care of women; to establish and maintain the highest possible standards for education; to foster the highest quality of practice; to promote high ethical standards in practice; to promote publications and encourage contributions to medical and scientific literature. ACOG has over forty standing committees to carry out its mission, including the Committee on Ethics. In November 2002, ACOG published a Committee Opinion addressing patents, medicine and the interests of patients.[4]

The Association for Molecular Pathology (AMP) is an international not-for-profit scientific education society representing over 1,300 physicians, doctoral scientists, and medical technologists who perform molecular diagnostic testing based on the applications of genomics and proteomics. AMP is committed to the advancement of clinical molecular diagnostic and prognostic medicine through education and

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[4] *See* Am. Coll. of Obstetricians & Gynecologists, *Patents, Medicine, and the Interests of Patients, in Ethics in obstetrics and gynecology* (ACOG Washington, D.C. 2d ed. 2004).

training of practitioners, physicians, laboratory and industrial scientists, and health care professionals involved in patient care and management. AMP supports the development of new technologies in molecular biology to be used in laboratory medicine, including diagnosis, treatment, and prognosis of genetic disorders, cancer, infectious diseases, identity and histocompatibility. AMP members are involved in every aspect of molecular diagnostic testing, administration and interpretation of molecular diagnostic tests, research and development, and education. AMP provides national leadership for the advancement of safe and effective practice and education for molecular diagnostic testing in the health care industry. In November 1999, AMP adopted a position statement opposing patents and licensing agreements that inappropriately limit clinical care, the use of medical procedures, medical education, and medical research.

The Association of American Medical Colleges (AAMC) is a non-profit organization representing all 125 allopathic medical schools in the United States, about 400 major teaching hospitals and health systems, and 94 academic and professional societies representing nearly 110,000 faculty members. AAMC's member institutions are at the forefront of medical education, research and research training, and health care innovation and delivery. AAMC members perform nearly 60% of the extramural research sponsored by the National Institutes of Health, and they partner with industry in discovering new and better approaches to the diagnosis, treatment, and prevention of human diseases. The AAMC is committed to the continuing improvement of health care and the Continuing Medical Education of physician practitioners based on sound scientific evidence. These goals require, and AAMC strongly supports, policies that promote the unfettered generation and dissemination of new scientific knowledge, the transfer of new technologies from university laboratories to social and commercial application, and the broadest possible sharing of scientific and medical

information in support of the advancement of science, patient care, and the health of the public.

The College of American Pathologists (CAP) has nearly 16,000 physician members, including 91% of all eligible board-certified pathologists. It is the world's largest medical society composed exclusively of pathologists, who are physicians who obtain and interpret data as the result of examination of tissues, blood, and other body fluids for diagnosis and patient care. The CAP also serves the laboratory community throughout the world. More than 6,000 laboratories are accredited by the CAP, and approximately 23,000 laboratories are enrolled in the College's proficiency testing programs.

MEDICAL AND ETHICAL BACKGROUND

The patent in this case, United States Patent No. 4,940,658 (the '658 patent), sets forth a method of testing for blood levels of the amino acid homocysteine using gas chromatography and mass spectrometry. The inventors used this method to study a correlation between elevated homocysteine and vitamin deficiencies. The results of their testing for this correlation are reported in the patent.

To assist this Court in understanding the '658 patent and how the enforcement of Claim 13 would negatively affect medical care and research, amici offer the following medical background. As this background will demonstrate, the test methods and scientific observations in the '658 patent did not emerge in a vacuum. They are part of a continuum of medical research and development aimed at improving patient care. Amici believe that the enforcement of a broad and unwarranted patent claim on the association between elevated levels of homocysteine and vitamin deficiencies would interfere substantially with the achievement of that goal and would raise important ethical issues.

A. The Nature Of And Tests For Homocysteine

Homocysteine is an amino acid[5] that is normally found in very small amounts in human blood, where it exists in multiple forms.[6] Well before the filing of the application for what became the '658 Patent, researchers understood the critical role of vitamins B_6, B_{12} (cobalamin) and folate (folic acid) in the metabolism of homocysteine and the impact of an individual's dietary intake of these vitamins on homocysteine levels.[7]

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[5] An amino acid is an organic compound containing an amino (NH_2) and a carboxyl (COOH) group. In the human body, amino acids are linked together to form proteins. An "essential" amino acid is one that is required for protein synthesis but cannot be made by humans and, therefore, must be supplied in the diet. *Dorland's Illustrated Medical Dictionary*, *available at* http://www.mercksource.com/pp/us/cns_hl_dorlands.html (last visited Dec. 14, 2005).

[6] Those forms include protein-bound homocysteine (about 70%), free homocysteine, the disulfide homocystine, and mixed homocysteine-cysteine disulfide. Together, these forms are referred to as total plasma (or serum) homocysteine, or as total homocysteine, [hereinafter "homocysteine"]. Am. Soc'y of Human Genetics/Am. Coll. of Med. Genetics, *Measurement and Use of Total Plasma Homocysteine*, 63 Am. J. Hum. Gen. 1541 (1998), *reaffirmed* by Am Coll. of Med. Genetics (Oct. 25, 2005).

[7] In humans, homocysteine is formed as an intermediary during the conversion of the essential amino acid methionine to the amino acid cysteine. In this metabolic pathway, in which homocysteine is both created and largely reconverted back to methionine, vitamins B_{12} and folate (as well as other enzymes and coenzymes) play a critical role. Impaired reactions in this pathway, because of defects in the required enzymes or the vitamin coenzymes, may result in an increased accumulation of homocysteine in the blood. *See generally* L.D. Fleisher & G.E. Gaull, *Methionine Metabolism in Man: Development and Deficiencies, in* 3 *Clinics in Endocrinology and Metabolism* 36 (H. Bickel ed., 1974). *See also* M.C. Higgenbottom, L. Sweetman & W.L. Nyhan, *A syndrome of methylmalonic aciduria, homocystinuria, megaloblastic anemia and neurological abnormalities in a vitamin B_{12}-deficient breast-fed infant of a strict vegetarian*, 299 N. Eng. J. Med. 317 (1978); D.A.

1. Early Research Into Homocysteine And Its Association With Disease

In 1963, an association between elevated homocysteine levels and human disease was shown by a finding of very high homocystine/homocystine concentrations in the urine of some children with mental retardation.[8] This condition, called homocystinuria, was shown to be caused by an inherited enzymatic error of homocysteine metabolism.[9] Among the clinical effects of this disorder was the occurrence of premature occlusive cardiovascular disease.

In 1969, Dr. Kilmer McCully described the vascular pathology in homocystinuria patients and suggested that the vascular damage was produced specifically by the accumulation of homocysteine or its derivatives.[10] During the next fifteen years, it was discussed and well documented that even a moderately elevated level of homocysteine is a strong independent risk factor for heart disease and stroke.[11]

By 1969, at least two articles had reported that elevated levels of homocyst(e)ine could result from a deficiency of vitamin B_{12}.[12] It also was shown, however, that the etiologies

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Hollowell et al., *Homocystinuria and organic aciduria in a patient with vitamin B_{12} deficiency*, 2 Lancet 1428 (1969).

[8] N.A.J. Carson et al., *Homocystinuria: a new inborn error of metabolism associated with mental deficiency*, 38 Arch. Dis. Child. 425 (1963).

[9] *Id.*

[10] K. McCully, *Vascular pathology of homocystinuria: Implications for the pathogenesis of arteriosclerosis*, 56 Am. J. Pathol. 111 (1969).

[11] *See, e.g.*, L.B. Brattstrom et al., *Moderate homocysteinemia – A possible risk factor for arteriosclerotic cerebro-vascular disease*, 15 Stroke 1012 (1982). K.S. McCully, *Homocysteine theory of arteriosclerosis: Development and current status*, 11 Atherosclerosis Rev. 157 (1983).

[12] Hollowell et al., *supra* note 6. M.C. Carey et al., *Homocystinuria. II. subnormal serum folate levels, increased folate clearance and effects of folic acid therapy*, 45 Am. J. Med. 26 (1968).

of elevated plasma homocysteine ("homocysteinemia" or "hyperhomocysteinemia") are complex and that several factors, both genetic and environmental, may contribute to elevated plasma homocysteine levels, even if an individual's vitamin intake is normal. These factors include chronic renal disease, alcoholism, drug-induced effects, and several different genetic abnormalities.[13]

2. Importance Of Tests For Homocysteine

Prior to 1985, there already were a variety of tests used to screen for elevated homocysteine levels. These included paper or thin layer chromatography, and quantitative amino acid analysis by standard or automated column chromatography.[14] While much of the testing was performed in an effort to diagnose and elucidate the basis of one or more genetic disorders known to cause elevated homocysteine levels, the potential relationship between vitamin deficiencies and elevated homocysteine levels had already been well-recognized and discussed among experts in the field.[15]

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[13] Am. Med. Ass'n, Report 5 of Council on Scientific Affairs, *Folic Acid Relationships to Spinal Closure Birth Defects and Adult Vascular Disease* (1995) [hereinafter "AMA Folic Acid Report"]. For example, about 0.5% of the U.S. population are carriers of the mutant gene that most frequently causes inherited homocystinuria, and these carriers may demonstrate elevated plasma homocysteine levels. S. Kang et al., *Hyperhomocyst(e)inemia as a risk factor for occlusive vascular disease*, 12 Ann. Rev. Nutr. 279 (1992). Further, 20% of all vegetarians also have moderate hyperhomocysteinemia. W. Herrmann et al., *Total homocystein, vitamin B_{12}, and total antioxidant status in Vegetarians*, 47 Clin. Chem 1094 (2001).

[14] Chromatography encompasses a group of analytical chemistry methods for the separation and purification of molecules in clinical samples. In general, it involves separating the various molecules in the sample based on molecular size, chemical properties, ionic charge, relative solubility, etc.

[15] *See* S.H. Mudd, *Homocystinuria: The Known Causes, in Inherited Disorders of Sulfur Metabolism* 204, 219 (N.A.J. Carson & D.N. Raine

It also was recognized, however, that the observed association between homocysteine and vitamins B_{12} and folate, although sensitive, is not specific. "[A]n animal with elevated levels of total homocysteine is likely to have one or both [vitamin B_{12} and folate] deficiencies, but the assay [of total homocysteine] does not distinguish between the two." '658 patent col.4 ll.20-23. Both folate and B_{12} deficiencies result in hyperhomocysteinemia, thus rendering the measurement of plasma homocysteine levels an ineffective tool to *diagnose* either folate deficiency or vitamin B_{12} deficiency. It was necessary to (a) perform a second assay, for the substance methylmalonic acid, in combination with the homocysteine assay, and then (b) compare total homocysteine levels to total methylmalonic acid levels in order to diagnose and distinguish among folate deficiency, vitamin B_{12} deficiency or a deficiency of both vitamins.

Today, several newer tests are available to measure total homocysteine in body fluids and tissues. These include analysis by gas chromatography/mass spectrometry (GC/MS) as described in the Patent and fluorescence polarization immunoassay (FPI) such as the method developed by Abbott Laboratories.[16] All of these tests provide clinicians with useful information by which they can screen patients for the risk of a variety of disorders, including vascular occlusive disease. None of these tests, however, alone or in combination, can definitively diagnose a deficiency of

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eds., 1971) (citing J.G. Hollowell et al., *Homocystinuria and organic aciduria in a patient with vitamin-B_{12} deficiency*, 2 Lancet 1428 (1969)); M.C. Higgenbottom, L. Sweetman & W.L. Nyhan, *supra* note 7.

[16] GC/MS combines the features of gas-liquid chromatography (to separate molecules) with mass spectrometry, which breaks each molecule down and identifies it. FPI is based on a competitive immunoassay that uses a fluorescent label. FPI requires neither the time nor expense involved in GC/MS procedures. For details of, and comparison between these methods, *see, e.g.*, J.B. Ubbink et al., *Comparison of three different plasma homocysteine assays with gas chromatography/mass spectrometry*, 45 Clin. Chem. 670 (1999).

vitamins B_6 or B_{12}, or of folic acid, because, *inter alia*, elevated homocysteine levels may be the result of several genetic, metabolic and/or nutritional abnormalities. Relying on the observed association between hyperhomocysteinemia and vitamin levels alone is not definitive.

3. Current Use Of Homocysteine Tests And Research Into Homocysteine

Today, tests for elevated levels of homocysteine are performed for a variety of medical reasons. It is well-accepted that even a mild elevation of plasma homocysteine is an independent risk factor for cardiovascular disease, peripheral arterial occlusive disease, stroke and venous thrombosis.[17] Many studies have demonstrated the causality of homocysteine's role in the development of vascular disease and suggested benefits from dietary supplementation.[18] As

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[17] *See, e.g.*, C.J. Boushey et al., *A quantitative assessment of homocysteine as a risk factor for vascular disease. Probable benefits from increasing folate intakes*, 274 JAMA 1049 (1994). R. Clarke et al., *Hyperhomocysteinemia: an independent risk factor for vascular disease*, 324 N. Eng. J. Med. 1149 (1991). I.M. Graham et al., *Plasma homocysteine as a risk factor for vascular disease (The European Concerted Action Project)*, 277 JAMA 1775 (1997). H. Refsum et al., *Homocysteine and cardiovascular disease*, 49 Ann. Rev. Med. 31 (1998). J.M. Scott, *Homocysteine and cardiovascular risk*, 72 Am. J. Clin. Nutr. 333 (2000).

[18] AMA Folic Acid Report. *See, e.g.*, Boushey et al., *supra* note 17. S.J. Moat et al., *Treatment of coronary heart disease with folic acid: is there a future?*, 287 Am. J. Physiol. H1 (2004). M. Coffey et al., *Reducing coronary artery disease by decreasing homocysteine levels*, 23 Crit. Care Nurse 25 (2003). M.T. Stauffenberg, *Hyperhomocysteinemia measured by immunoassay: A valid measure of coronary artery atherosclerosis*, 128 Arch. Pathol. Lab. Med. 1263 (2004). *But see* M. Villar-Fidalgo et al., *Prevalence of hyperhomocysteinemia and associated factors in primary health care*, 125 Med. Clin. (Barc) 487 (2005) (suggesting the need for further research to determine whether homocysteine actually adds predictive power to measurements of cardiovascular risk).

many as 50% of patients suffering from stroke and other atherothrombotic diseases have elevated homocysteine levels.[19] Thus, plasma homocysteine levels are frequently measured to help estimate an individual's risk for one or more of these disorders.[20]

As a result of continuing investigations into, and new knowledge regarding, the relationships between levels of homocysteine and various diseases, it was estimated in 1999 that the number of homocysteine tests could grow to exceed 100 million per year.[21] The vast majority of these tests will

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[19] AMA Folic Acid Report. Am. Soc'y of Human Genetics/Am. Coll. of Med. Genetics, *supra* note 6.

[20] Recently, studies also have demonstrated an association between hyperhomocysteinemia and a number of age-related medical disorders, including cognitive impairment and Alzheimer's disease, osteoporosis-related fractures, and brain infarction, as well as the development of diabetes in certain women, and early pregnancy loss. *See, e.g.*, H.-K. Kuo et al., *The role of homocysteine in multisystem age-related problems: A systematic review*, 60 J. Gerontol. A. Biol. Sci. Med. Sci. 1190 (2005); K.L. Tucker et al., *High homocysteine and low B vitamins predict cognitive decline in aging men: the Veteran Affairs Normative Aging Study*, 82 Am. J. Cli. Nutr. 627 (2005); M. Folin et al., *A cross-sectional study of homocysteine-, NO-levels, and CT-findings in Alzheimer dementia, vascular dementia and controls*, 6(4) Biogerontology 255 (2005); R.R. Mclean et al., *Homocysteine as a predictive factor for hip fracture in older persons*, 350 N. Eng. J. Med. 2042 (2004). J.B.J. van Meurs et al., *Homocysteine levels and the risk of osteoporatic fracture*, 350 N. Engl J. Med. 2033 (2004); N.K. Kim et al., *Hyperhomocysteinemia as an independent risk factor for silent brain infarction*, 61 Neurology 1595 (2003); N.H. Cho et al., *Elevated homocysteine as a risk factor for the development of diabetes in women with a previous history of gestational diabetes mellitis: a 4-year prospective study*, 28(11) Diabetes Care 2750 (2005); W.L.D.M. Nelen et al., *Homocysteine and folate levels as risk factors for recurring early pregnancy loss*, 95 Obstet. Gynecol. 519 (2000).

[21] *American Heart Association Recommends Homocysteine Testing, at* http://www.cfonews.com/cct/c010599y.htm (last visited Dec. 14, 2005). "'It will probably soon be as common to have one's homocysteine levels

be performed to determine an individual's risk of developing heart disease or stroke. Nevertheless, the scientist or physician who views laboratory results showing hyperhomocysteinemia may, in fact, recall the association between such a result and one or more vitamin deficiencies. On that basis, the physician may, depending on the circumstances, choose to order one or more additional tests that are needed to diagnose which particular vitamin, if any, a patient may need as a supplement to his or her diet.

B. Ethical Concerns With Patents On Scientific Principles

The associations submitting this brief recognize that health-care-related patents can enhance the provision of high-quality and cost-effective medical care. The financial incentive that patents offer supports the expensive and uncertain research required to identify, test, and gain approval for new pharmaceutical products, medical devices, diagnostic testing kits, and comparable applications of scientific fact and principle that provide novel advances in medical treatment. The associations recognize that, without patent protection, many exceptionally valuable advances in medical care may not otherwise occur. In this respect, the patent system has served, and can continue to serve, patients and the medical profession well.

Patents on basic scientific principles, however, raise more difficult issues. Such patents ultimately erode the quality of patient care by limiting the knowledge physicians may use to diagnose and treat their patients.

Physicians have a longstanding ethical obligation to advance and share useful medical knowledge with patients and physicians. The principle is embodied both in Principle V of the AMA's Principles of Medical Ethics, and in Opinion 9.08 of the AMA's Code of Medical Ethics. Principle V

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checked as it is now to have one's cholesterol level checked.'" *Id.* (quoting Dr. Malinow of the Oregon Health Sciences University).

states that a "physician shall continue to study, apply and advance scientific knowledge," and "make relevant information available to patients, colleagues, and the public."[22]

Opinion 9.08 of the Code of Medical Ethics of the AMA elaborates upon this basic principle. It states, in pertinent part, that:

> Physicians have an obligation to share their knowledge and skills and to report the results of clinical and laboratory research. . . . The intentional withholding of new medical knowledge, skills and techniques from colleagues for reasons of personal gain is detrimental to the medical profession and to society and is to be condemned.[23]

Discovery of a basic scientific principle – one that could be useful to others in devising any number of useful medical applications or to a physician in reaching a diagnosis and treating a patient – is a quintessential example of the kind of medical knowledge that physicians are obliged freely to share. To interpret the patent laws to make scientific principles eligible for patent protection is not only unnecessary, but threatens to undermine, rather than promote, effective patient care. By allowing a private party to restrain the use of a basic scientific principle, patents on scientific principles hinder the efforts of others to develop or employ new and superior medical advances that would build on that principle. By creating concerns about inducing infringement, such patents deter laboratories and others from disseminating basic scientific information that would be useful to physicians in providing cost-effective and high-quality care to their

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[22] Available at www.ama-assn.org/ama/pub/category/2512.html (last visited Dec. 21, 2005).

[23] Available at www.ama-assn.org/apps/pf_new/pf_online?f_n=browse&doc=policyfiles/HnE/E-9.08.HTM (last visited Dec. 21, 2005).

patients. Such patents also interfere with a physician's ability to provide the diagnostic care a patient needs. In short, patents on scientific principles interfere with the development of medical advances and the provision of effective patient care.

SUMMARY OF ARGUMENT

Claim 13 states, in its entirety:

> A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> assaying a body fluid for an elevated level of total homocysteine; and
>
> correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

'658 patent col.11 ll.58-65.

The Federal Circuit accepted that step one in claim 13 covers any "assay" or test for homocysteine levels, whether or not that test was described in any fashion in the specification or known in the prior art. Pet. App. 26a-27a. The Federal Circuit construed step two to "only require[] association of homocysteine levels with vitamin deficiencies." *Id.* at 8a. As a result, Claim 13 is practiced whenever a physician orders a test for homocysteine, no matter what type of test is ordered, and then considers the association of homocysteine levels with vitamin deficiency. The Court of Appeals accepted, as evidence sufficient to prove inducement, testimony that every physician who reviews results of a homocysteine test will consider the association with vitamin deficiency. *Id.* at 18a. As a result, every physician who orders and reviews the results of a test for levels of homocysteine practices Claim 13.

Claim 13 of the '658 patent improperly claims subject matter that is outside the scope permitted by 35 U.S.C. § 101. Claim 13 patents the association that any physician would

make between test results showing elevated levels of homocysteine and vitamin deficiency. Claim 13 is not limited to any particular method of testing homocysteine levels, and it does not require a physician to perform any act other than simply to order a test and read the results. Claim 13 therefore patents a scientific principle – that elevated homocysteine levels are associated with vitamin deficiency – rather than a useful application of that principle. Under long-settled limits on the permissible scope of patentable subject matter, Claim 13 is invalid.

Claim 13 also illustrates the importance of enforcing this limitation. Patents on scientific principles are precluded because they are inherently overbroad, and because they operate to chill, rather than to promote, the progress of science and the useful arts and, as in this case, the sound practice of medicine. Claim 13, as construed by the Federal Circuit, displays each of these defects. Its enforcement undercuts the objectives of the patent system as envisioned by the framers of the Constitution and as enacted by Congress.

ARGUMENT

A. Claim 13 Improperly Claims Non-Patentable Subject Matter.

The Constitution grants Congress broad power to enact legislation to "promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." U.S. Const. art. I, § 8, cl. 8. Congress promptly exercised this power in the Patent Act of 1790. "[A]uthored by Thomas Jefferson," *Diamond* v. *Chakrabarty*, 447 U.S. 303, 308 (1980), the Act broadly defined the scope of matters that were subject to patent as "any new and useful art, machine, manufacture or composition of matter, or any new or useful improvement [thereof]." Act of Feb. 21, 1793, ch. 11, § 1, 1 Stat. 318, 319. Congress did not alter this language until 1952 when, in recodifying the patent laws, it

replaced the word "art" with "process." See Act of July 19, 1952, ch. 950, § 101, 66 Stat. 792, 797. Although Congress described its intent, in a Committee Report to the 1952 Act, to have Section 101 "include anything under the sun that is made by man,"[24] the inclusion of processes was not new, because the term "art" had previously been construed to include a "process." See *Diamond* v. *Diehr*, 450 U.S. 175, 182 (1981).

The scope of patentable subject matter, although broad, is not limitless. "The laws of nature, physical phenomena, and abstract ideas have been held not patentable." *Chakrabarty*, 447 U.S. at 309. As the Court has explained by illustration, "Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity. Such discoveries are 'manifestations of . . . nature, free to all men and reserved exclusively to none.'" *Id.* (omission in original) (quoting *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)).

Beginning in the 1850s, this Court has repeatedly held and observed that Congress has not permitted individuals to obtain exclusive ownership of laws of nature, natural phenomena, or abstract ideas. See *LeRoy* v. *Tatham*, 55 U.S. (14 How.) 156 (1852) (invalidating patent because a scientific principle is unpatentable, and all that remained was a combination of machinery known in the prior art); *Chakrabarty*, 447 U.S. at 309 (citing cases). For example, the Court invalidated the patent in *Funk* because the patentee had discovered "'only some of the handiwork of nature.'" *Id.* at 310 (quoting *Funk*, 333 U.S. at 131). By contrast, it upheld the patent in *Chakrabarty* because the patentee claimed not "a hitherto unknown natural phenomenon, but . . . a nonnaturally occurring manufacture or composition of matter." *Id.* at 309.

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[24] S. Rep. No. 82-1979, at 5 (1952), *reprinted at* 1952 U.S.C.C.A.N. 2394, 2399; H.R. Rep. No. 82-1923, at 6 (1952).

Although Claim 13 is cast in the format of a two-step "process" claim, it is indistinguishable from a scientific principle. It simply recites the fact that test results showing elevated levels of homocysteine are associated with vitamin deficiency. Claim 13 is therefore invalid because it claims subject matter that is not eligible for patent protection. That is true of each step, as well as of the claim as a whole. Claim 13 combines an abstract idea (testing, by any method) with a scientific principle (that high homocysteine levels are associated with vitamin deficiencies). Had these steps contained meaningful limitations, a valid claim might have emerged. But the Court of Appeals found no such limitation in either step.

Step one of claim 13 covers *any* test for homocysteine levels, including tests disclosed in the prior art, and tests not yet invented. It is not supported by any written description in the specification. Indeed, it is difficult to imagine how any specification could describe every method, past, present, and future, for testing homocysteine levels. Certainly this specification made no such attempt. Step one thus merely recites an "abstract idea" – that of testing for homocysteine levels – rather than a particular method for doing so.[25]

The Federal Circuit construed step two of claim 13 to cover any "association of homocysteine levels with vitamin deficiencies." Pet. App. 8a; see also *id.* at 12a. The Court of Appeals expressly refused to place any limits on the nature of that association or the acts required to establish it.

For example, the court declined to require any evaluation of the specific levels of homocysteine found, or even that homocysteine levels be elevated above some normal level or

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[25] The lack of a supporting written description can also be grounds to invalidate a claim under 35 U.S.C. § 112 paragraph 1. As discussed below, the lack of an adequate written description is characteristic of an attempt to patent abstract ideas, scientific principles, or laws of nature. *See infra* Part B.

range. Pet. App. 12a. The court also declined to require any step to confirm a diagnosis of vitamin deficiency, to identify which vitamin, if any, the patient needs, or to take any other step to associate the patient's condition with any particular "abnormalities." *Id.* at 10a. The court's construction of step two was so broad that the physician need take no step other than review the results of the test. "The correlating step *is a simple conclusion* that a cobalamin/folate deficiency exists *vel non* based on the assaying step." *Id.* at 18a (first emphasis added). The correlating step occurs automatically when the physician, aware of the "association," reads the test result. Or, to borrow from Descartes' famous maxim, "I think, therefore I" infringe Claim 13.

The Court of Appeals thus construed Claim 13 to cover a scientific principle: that elevated homocysteine levels are associated with vitamin deficiency. This fact is not part of a series of acts which form a process. It is the process. "[A] scientific truth," however, "is not a patentable invention." *Mackay Radio & Tel. Co.* v. *Radio Corp. of Am.*, 306 U.S. 86, 94 (1939). "'He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes.'" *Diehr*, 450 U.S. at 188 n.11.

Section 101 does not permit the patenting of a basic scientific principle even when knowledge of that principle proves exceptionally helpful in treating a patient. The venerable case of *Morton* v. *New York Eye Infirmary*, 17 F. Cas. 879 (C.C.S.D.N.Y. 1862) (No. 9865), illustrates the point well. The court invalidated a patent on the seminal discovery that ether was an effective anesthetic for surgery. The court acknowledged the testimony of "distinguished surgeons" who ranked the idea of employing ether in surgery as "among the great discoveries of modern times" and lauded the patentee as one of "the greatest benefactors of mankind." *Id.* at 883. But both ether itself, and the scientific fact that inhaling ether sedates a human, were well-known. *Id.* at 882. The patent claimed no definite process for administering

ether, because the amount of ether to be given to a patient was left to the "discretion of the operator." *Id.* at 883. It thus amounted to a patent on the scientific fact that ether reduces pain during surgery which, while a useful discovery, was not patentable. *Id.*

Claim 13 is defective in the same way as the ether patent. Claim 13 identifies a useful purpose for measuring levels of homocysteine (*i.e.*, to check for vitamin deficiency), but does not claim any new method for such measuring. It fails to bring its discovery of the association of homocysteine levels and vitamin deficiency "into practical action," which is essential to patentability. *Id.* at 881-83. See *Mackay Radio*, 306 U.S. at 94 ("While a scientific truth . . . is not patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be."); *LeRoy* v. *Tatham*, 55 U.S. (14 How.) at 175 ("The elements of the power exist; the invention is not in discovering them, but in applying them to useful objects.").

Claims 1-12 do not share this fundamental defect. Those claims recite specific methods for testing for homocysteine levels that are limited by the claim language and supported by a written description in the specification. In those claims, the patentees sought to bring "into practical action" their discovery about the association between homocysteine levels and vitamin deficiency. By devising and claiming a new method for testing homocysteine levels, they at least facially sought to claim patentable subject matter.

In Claim 13, however, the patentees overreached. They attempted to patent any physician's consideration of a scientific principle: that a patient's test results showing elevated homocysteine levels are associated with vitamin deficiency. A scientific fact – even if it is quite useful – is not patentable subject matter. For this reason, claim 13 is invalid.

B. Claim 13 Is Overbroad.

One important reason why patents on natural phenomena, scientific principles, and abstract ideas have long been held outside the scope of patentable subject matters is that such patents are inherently overbroad. They claim any method of using a fact or idea for a given purpose. Yet their specifications do not, and cannot, purport to describe all such methods. Such claims are now often rejected as lacking a written description sufficient to support the claim "under the first paragraph of § 112." *In re Hyatt*, 708 F.2d 712, 715 (Fed. Cir. 1983). Claim 13 properly should have been invalidated under this provision as well. The problem of overbreadth is inherent in a patent on a scientific principle or abstract idea.

The most famous example is *O'Reilly* v. *Morse*, 56 U.S. (15 How.) 62 (1853).[26] At issue was Samuel Morse's patent on the electro-magnetic telegraph – a patent remarkably similar in its sequence of claims to the patent at issue here.

The first seven claims of Morse's patent claimed a specific apparatus and process for a telegraph. These claims were upheld. In the eighth claim, however, Morse sought more broadly to patent "'the use of the motive power of the electric or galvanic current, which I call electro-magnetism, *however developed* for marking or printing intelligible characters, signs, or letters, at any distances.'" *Id.* at 112 (emphasis added). The Court invalidated this claim.

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[26] Another well-known example is *Wyeth* v. *Stone*, 30 F. Cas. 723 (C.C.D. Mass. 1840) (No. 18,107) (Story, J.). There the patentee invented one method of cutting ice blocks of a uniform size other than by hand, but sought to claim any such method. The court held that "[s]such a claim is utterly unmaintainable in point of law." *Id.* at 727. "No man can have a right to cut ice by all means or methods, or by all or any sort of apparatus, although he is not the inventor of any or all of such means, methods, or apparatus." *Id.*

The Court recognized that Morse's eighth claim, if allowed, would effectively grant Morse ownership of the idea of using electric current to print at a distance. That is because, under claim 8, it "matter[ed] not by what process or machinery the result is accomplished." *Id.* at 113. Claim 8 would thus cover the work of "some future inventor" who, "in the onward march of science, may discover a mode of writing or printing at a distance by means of the electric or galvanic current, without using any part of the process or combination set forth in plaintiff's specification." *Id.* Such an invention "may be less complicated – less liable to get out of order – less expensive in construction," and yet if covered by this patent might not be made available to the public. *Id.* It would give Morse "an exclusive right to use a manner and process which he has not described and indeed had not invented, and therefore could not describe when he obtained his patent." *Id.*

The same problem of overbreadth that led to the invalidation of Morse's eighth claim should also invalidate claim 13 of the '658 patent. The patentees here in claim 13, like Morse in claim 8, have written claims so broadly that they swallow all the claims that precede them. "Indeed, if the eighth claim of the patentee can be maintained, there was no necessity for any specification, further than to say that he had discovered that, by using the motive power of electro-magnetism, he could print intelligible characters at a distance." *Id.* at 119. Similarly, if claim 13 is maintained as construed, then there is no need for such claims as 1-12 or any specification, other than to say that the patentees had discovered, by measuring homocysteine levels, that they could detect a vitamin deficiency.

The basic defect in the claim challenged in each case is the same. Like claim 8 of Morse's patent, claim 13 of the '658 patent grants the patentees exclusive rights in a process they neither described nor invented. Just as Morse was not permitted to patent any method for using electric current to

send telegrams, these patentees ought not be permitted to patent any method for using homocysteine levels to determine a vitamin deficiency.

C. Patents Solely On Scientific Facts Stifle Innovation And Conflict With Patient Care.

There is a final basic reason why scientific facts, without more, have properly been deemed outside the scope of patentable subject matter. Basic scientific facts, untethered to a novel application, "are part of the storehouse of knowledge of all men." *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948). They are elements of useful inventions, not inventions in themselves. Ensuring wide dissemination and free access to such facts is therefore essential to scientific progress.

The discussion above of the history of research into homocysteine illustrates that these patentees are neither the first nor the last to consider the relationship of homocysteine to human health. Others recognized that elevated homocyst(e)ine levels were associated with a vitamin deficiency before the patentees did, see *supra* p. 8 and note 12 and p. 9 and note 14, and the ability to test for homocysteine levels was also well-established, see *supra* p. 9. Since the patentees' work, other scientists have made, and continue to make, important contributions to our ability to measure levels of homocysteine and our understanding of its significance as an indicator of various diseases and conditions. See *supra* pp. 10-12 and notes 16-20. The range of important and ongoing research is vast, and the need for ready access to and ability to use basic facts, such as a relationship between levels of an amino acid and vitamins, is essential to those efforts. Allowing private parties to own such facts stifles scientific progress and obstructs patient care.

Here, for example, disclosure of the scientific fact that vitamin deficiencies (and, more importantly, heart disease and other conditions) are associated with elevated levels of

homocysteine created an incentive for laboratories to develop new, fast, and inexpensive ways of testing for homocysteine. But if the person who discovers such an association is permitted to patent any means of testing for it, then that patentee may "shut[] the door" to the development or use of such new tests, and discourage further research and development. *Morse*, 56 U.S. (15 How.) at 113.

This case also shows how the patentee may go further still to render unlawful the dissemination of those basic facts. Here, for example, the Court of Appeals held that petitioner had induced infringement through the publication of medical articles. Without evincing any concern, the court states:

> LabCorp publishes both Continuing Medical Education Articles as well as a Directory of Services that are specifically targeted to the medical doctors ordering the LabCorp assays. These publications state that elevated total homocysteine correlates to cobalmin/folate deficiency and that this deficiency can be treated with vitamin supplements. LabCorp's articles thus promote total homocysteine assays for detecting cobalamin/folate deficiency.

Pet. App. 15a. According to the Court of Appeals, therefore, a laboratory can induce infringement of a patent – and thereby expose itself to millions of dollars in damages and penalties – simply by informing physicians, in an article for continuing medical education, that high levels of an amino acid signal a risk to patient health. Such a ruling obviously chills the dissemination of basic facts – which, as shown above, is central to sound medical practice, and is essential for physicians to stay abreast of continuing homocysteine-related research. See *supra* pp. 13-15. Yet a fundamental objective of the patent system, and a principle reason why society is willing to confer a patent monopoly, is to promote the publication of inventions.

The Federal Circuit's ruling, if allowed to stand, would support the patent eligibility of other claims that would distort patent law beyond recognition. By discovering a previously unknown correlation between obesity and illness, for example, a researcher could obtain a patent on the process of stepping on a scale and thinking of that illness. Any entity that made or sold scales, and that dared to mention that correlation in a brochure, would then be liable for intentionally inducing infringement. Such a result is unthinkable – except under the logic of the decision below.

A final indication that the Court of Appeals erred is in the inability of any physician who knows of the association between homocysteine and vitamin deficiency to avoid practicing claim 13.[27] There can be no design around a scientific fact. For example, the patentees are able to hinder the use of homocysteine tests even when, as shown above (see *supra* pp. 11-13), the purpose is to test for a risk factor for heart disease rather than for vitamin deficiency.

A physician who learns – from the medical literature, colleagues, continuing medical education, or other public sources – of the naturally occurring association between homocysteine and vitamin deficiency cannot put that knowledge out of mind. Knowledge of basic scientific facts such as a correlation between a test result and a possible disease state is essential to the practice of medicine. Once learned, such knowledge remains.

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[27] Congress has exempted physicians from liability for direct infringement for "the performance of a medical or surgical procedure on a body," but not for "the practice of a process in violation of a biotechnology patent." 35 U.S.C. § 287(c)(2)(A). Section 287(c)(4) is, by its own terms, inapplicable to patents with applications filed prior to September 30, 1996. The '658 patent application was filed in 1986. Thus, the question of whether a physician who requests a test of a bodily fluid, and then considers the results in the light of medical knowledge, thereby performs "a medical procedure . . . on a body" within the meaning of § 287(c)(2)(A) was not addressed below and is not before this Court.

Thomas Jefferson aptly described this difficulty in allowing patents upon ideas:

> If nature has made any one thing less susceptible than all others of exclusive property, it is the action of the thinking power called an idea, which an individual may exclusively possess as long as he keeps it to himself; but the moment it is divulged, it forces itself into the possession of every one, and the receiver cannot dispossess himself of it. [28]

Nor should he. A physician is ethically obliged to consider test results in light, among other things, of current medical knowledge. Such is the nature of a scientific fact: Once known, it must be considered. And as it must be considered, it ought not be patentable.

Respect for our nation's patent laws and the developments that they have promoted should not lead to an extension of those laws to confer a statutory monopoly that Congress did not intend. In *62 Cases of Jam* v. *United States*, 340 U.S. 593, 600 (1951), this Court stated that: "In our anxiety to effectuate the congressional purpose of protecting the public, we must take care not to extend the scope of the statute beyond the point where Congress indicated it would stop." Similarly here, this Court should take care not to extend the scope of subject matter eligible for a patent beyond the point that Congress indicated that it would stop.

As this case demonstrates, upholding a claimed patent on a scientific fact would directly undercut the goal of making diagnostic and treatment advances widely accessible at minimal cost to patients. This would be an unfortunate result if Congress had so ordained. But it is without warrant where,

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[28] Letter from Thomas Jefferson to Isaac McPherson (Aug. 13, 1813) *reprinted in* The Letters of Thomas Jefferson: 1743-1826, *available at* Electronic Text Center, University of Virginia Library.

as here, Congress did not write the patent laws to permit such consequences.

CONCLUSION

For the foregoing reasons, the judgment should be reversed.

Respectfully submitted,

JACK R. BIERIG*
LYNN D. FLEISHER
SIDLEY AUSTIN BROWN
& WOOD LLP
One South Dearborn Street
Chicago, IL 60603
(312) 853-7000

Counsel for Amici Curiae

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* Counsel of Record

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IN THE

Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS, dba LabCorp,

Petitioner,

v.

METABOLITE LABORATORIES, INC., *et al.*,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

AMICUS CURIAE BRIEF OF THE ASSOCIATION OF THE BAR OF THE CITY OF NEW YORK IN SUPPORT OF NEITHER PARTY

CATRIONA M. COLLINS
Counsel of Record
COWAN LIEBOWITZ & LATMAN, P.C.
1133 Avenue of the Americas
New York, NY 10036-6799
(212) 790-9200

PETER A. SULLIVAN
Chair of the Committee on Patents of The Association of the Bar of the City of New York
HUGHES HUBBARD & REED LLP
One Battery Park Plaza
New York, NY 10004
(212) 837-6000

Counsel for Amicus Curiae

December 23, 2005

198590

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INTEREST OF *AMICUS CURIAE*

Amicus Curiae the Association of the Bar of the City of New York is a private, non-profit organization of more than 22,000 attorneys, judges and law professors who are professionally involved in a broad range of law-related activities. Founded in 1870, the Association is one of the oldest bar associations in the United States. The Association seeks to promote legal reform and to improve the administration of justice at the local, state, federal and international levels through its more than 180 standing and special committees. The Committee on Patents ("the Committee") is a long-established standing committee of the Association, and its membership reflects a wide range of corporate, private practice and academic experience in patent law.[1]

DISCUSSION

This Court granted *certiorari* on Question No. 3 in the Petitioner's brief, which reads as follows:

> Whether a method patent setting forth an indefinite, undescribed and non-enabling step directing a party simply to "correlate" test results can validly claim a monopoly over a basic scientific relationship used in medical treatment

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1. The parties have consented to the filing of this brief *amicus curiae* and letters of consent have been filed in accordance with Rule 37.3. Pursuant to Rule 37.6, *amicus* represents that this brief was not authored in part or in whole by counsel for any party, and that no person or entity other than *amici* has made a monetary contribution to the preparation or submission of this brief.

> such that any doctor necessarily infringes the patent merely by thinking about the relationship after looking at a test result.

(Petr.'s Br. 1.)

The Court invited the Solicitor General to file a brief expressing the views of the United States as to whether the patent claim at issue covers patentable subject matter under *Diamond v. Diehr*, 450 U.S. 175 (1981):

> Respondent's patent claims a method for detecting a form of vitamin B deficiency, which focuses upon a correlation in the human body between elevated levels of certain amino acids and deficient levels of vitamin B. The method consists of the following: First, measure the level of the relevant amino acids using any device, whether the device is, or is not, patented; second, notice whether the amino acid level is elevated and, if so, conclude that a vitamin B deficiency exists. Is the patent invalid because one cannot patent "laws of nature, natural phenomena, and abstract ideas"? *Diamond v. Diehr*, 450 U.S. 175, 185 (1981).

The patent in suit, U.S. Patent No. 4,940,658 ("the '658 patent") is directed to methods for detecting deficiencies of cobalamin (vitamin B12) and folate (folic acid). The inventors discovered a relationship between elevated levels of total homocysteine and a deficiency in either cobalamin or folate. *See Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1358 (Fed. Cir. 2004). The inventors also developed a test to identify which particular

vitamin is deficient using methylmalonic acid (the panel test) and this test is the subject of other claims of the patent not at issue here. *Id.*

Claim 13 of the '658 patent reads as follows:

> A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> > Assaying a body fluid for an elevated level of total homocysteine;
> >
> > and correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

The jury found claim 13 to be valid and infringed. At trial, the petitioner argued that the claim was invalid because it was anticipated by prior art under Section 102; was obvious in light of the prior art under Section 103; did not "distinctly claim" the invention under Section 112, second paragraph; and did not satisfy the written description requirement of section 112, first paragraph. 370 F.3d at 1359, 1366-67.

The patent holders argued at trial that doctors were direct infringers because they performed one of the steps recited in the claim, namely the "correlating step," and that LabCorp induced doctors to infringe by performing a test for total homocysteine and publishing information to the effect that an elevated level of total homocysteine correlates with cobalamin or folate deficiency. *Id.* at 1365. The record suggests that any competent doctor will necessarily perform the second "correlating step" when he receives the results of

any total homocysteine assay because it would be malpractice for a doctor to receive a total homocysteine assay without determining cobalamin/folate deficiency. *Id.* at 1364.

SUMMARY OF ARGUMENT

The standards for determining whether a patent claim covers patentable subject matter as enunciated in *Diamond v. Diehr* should be reaffirmed by the Court.[2] Reiteration of the Court's holding in *Diehr* is timely because recent statements by the United States Court of Appeals for the Federal Circuit concerning the analysis of patent claims that may implicate laws of nature have deviated from *Diehr*. In particular, the scope of the patent claim is an essential part of the analysis under *Diehr*. The examination of patentable subject matter under Section 101 should not be confused or conflated with an analysis of the other requirements for patentability under the Patent Act. The analysis under Section 101 should be treated as a separate threshold issue, as required by *Diehr*. The circumstances in which a Section 101 analysis is needed should not be restricted because it is impossible to predict the advances in technology that may make a Section 101 analysis necessary.

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2. While some amicus briefs in this case may raise the issue of the recent abandonment by the United States Patents and Trademark Office of its "technological arts" test for examining business method patents under Section 101, the Committee does not believe that the issue is raised in this case, nor that this case is a good vehicle to examine that issue.

ARGUMENT

I. THE STANDARDS FOR EVALUATNG PATENTABLE SUBJECT MATTER ENUNCIATED IN *DIEHR* ARE CLEAR AND SHOULD BE REAFFIRMED.

In enacting the Patent Act, Congress intended statutory subject matter to "include anything under the sun that is made by man." S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952), H.R. Rep. No. 1923, 82d Cong., 2d Sess., 6 (1952), *Diamond v. Diehr*, 450 U.S. at 182. Under Section 101 of the Patent Act a new and useful process, machine, manufacture or composition of matter qualifies as patentable subject matter. 35 U.S.C. § 101 (2000).

Although Section 101 defines broad categories of patentable subject matter, it does not embrace every new discovery. It is well established that laws of nature, natural phenomena and abstract ideas remain in the public domain and cannot be the subject of a patent, even to one who is the first to identify them. *Diehr*, 450 U.S. at 185; *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980); *Parker v. Flook*, 437 U.S. 584, 589 (1978), *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972), *Funk Bros. Seed Co. v. Kalo Inoculant* Co., 333 U.S. 127, 130 (1948), *Mackay Radio & Tel. Co. v. Radio Corp. of Am.*, 306 U.S. 86, 94 (1939).

But it is also established by *Diehr* and earlier cases that the mere fact that a patent claim recites a law of nature does not necessarily render the claim unpatentable: "It is now commonplace that an application of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection." *Diehr*, 450 U.S. at

187; *see also Flook*, 437 U.S. at 590 ("[A] process is not unpatentable simply because it contains a law of nature."). Thus the first to discover a law of nature or natural phenomenon can obtain a patent for a practical application of his discovery. But this does not end the inquiry under Section 101. It must still be determined whether the patent claim is merely seeking patent protection for the law of nature in the abstract. *Diehr*, 450 U.S. at 191.

Diehr identifies two inquiries to determine whether a claim that is directed to a practical application of a law of nature covers the law of nature itself. The first inquiry is whether the claim preempts all practical uses of the law of nature. In *Diehr*, the Court found that the claimed process of curing synthetic rubber, using as part of the process a mathematical equation, did not "pre-empt the use of that equation" but permissibly foreclosed the use of the equation only in conjunction with all of the other steps in the claimed process. *Id.* at 187. *Compare Gottshalk v. Benson*, 409 U.S. 63, 72 (holding that a patent claim that "wholly pre-empts" a mathematical formula used in a general purpose digital computer is directed solely to a mathematical algorithm, and therefore does not define statutory subject matter under Section 101). The Court found the mathematical process claimed in *Benson* "so abstract and sweeping as to cover both known and unknown uses of the BCD [binary coded decimal] to pure binary conversion." 409 U.S. at 68, *citing O'Reilly v. Morse*, 56 U.S. (How.) 62, 113 (1852).

The preemption inquiry under *Diehr* and *Benson* thus necessarily involves an examination of the breadth of the claim. Nonetheless, the Federal Circuit stated recently that

an examination of the scope of the patent claim is not a proper part of a Section 101 analysis:

> [T]he claimed invention is without question a "composition of matter" or an article of "manufacture" within the terms of § 101. Accordingly, the claimed invention represents subject matter eligible for patent protection under § 101. **With that conclusion, the inquiry under § 101 ends... The scope of the claims is not relevant to subject matter eligibility. Subject matter does not take on a different eligibility status with adjustments in the scope of the proposed claim.**

SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1342 (Fed. Cir. 2005) (emphasis added).

While this statement by the Federal Circuit in *SmithKline* might have been intended to apply only to patent claims which do not implicate a law of nature, the statement *per se* is incorrect under *Diehr*. If this restrictive view of the scope of a patentable subject matter inquiry under Section 101 is followed, it could lead to the improper endorsement of a claim covering a law of nature, in contravention of *Diehr*.

Even if it is found that the claim does not preempt the law of nature at issue, *Diehr* still requires an examination of whether the claim contains merely an "insignificant addition" to the law of nature. In *Diehr*, the Court explained that in *Flook*, it had rejected "the argument that because all possible uses of the mathematical formula were not pre-empted, the

claim should be eligible for patent protection." *Diehr*, 450 U.S. at 193 n.14. The Court further explained as follows:

> A mathematical formula as such is not accorded the protection of our patent laws, *Gottschalk* v. *Benson*, 409 U.S. 63 (1972), and this principle cannot be circumvented by attempting to limit the use of the formula to a particular technological environment. *Parker* v. *Flook*, 437 U.S. 584 (1978). **Similarly, insignificant postsolution activity will not transform an unpatentable principle into a patentable process.**

Id. at 191-192 (emphasis added).

The inquiry under Section 101 as to whether the claim comprises merely an "insignificant addition" to the law of nature is not to be confused or conflated with the prior art-based anticipation and obviousness inquiries under Sections 102 and 103. In *Diehr*, the Court made it clear that the issue of whether a patent is directed to patentable subject matter under Section 101 is a threshold issue, separate from the analysis of patentability under other sections of the Patent Act:

> It has been urged that novelty is an appropriate consideration under § 101. Presumably, this argument results from the language in § 101 referring to any "new and useful" process, machine, etc. Section 101 however, is a general statement of the type of subject matter that is eligible for patent protection "subject to the conditions and requirements of this title." Specific conditions for patentability follow and § 102

> covers in detail the conditions relating to novelty. The question therefore of whether a particular invention is novel is "wholly apart from whether the invention falls into a category of statutory subject matter."

Id. at 189-190 (citations omitted).[3]

Recently, the Federal Circuit in *EMI Group North America, Inc. v. Cypress Semiconductor Corp.*, 268 F.3d 1342 (Fed. Cir. 2001), suggested that a law of nature which is recited in a claim should be treated as if it were prior art. The court in *EMI* stated that the "recitation of a law of nature does not distinguish a claim from prior art." 268 F.3d at 1351, *citing Funk Bros. Seed Co.*, 333 U.S. at 130. This statement is contrary to this Court's holding in *Funk Bros.* as clarified by *Diehr*. While the recitation of a law of nature that is inherently present in the prior art will not distinguish a claim from the prior art, the Federal Circuit's broad statement in *EMI* incorrectly suggests that any law of nature, even one that is not inherent in the prior art, should be treated as if it were prior art under Section 102. In *Diehr*, the Court dispelled this reading of its prior holdings in *Funk Bros.* and *Flook*, pointing out that this interpretation "would, if carried to its extreme, make all inventions unpatentable because all inventions can be reduced to underlying principles of nature which, once known, make their implementation obvious." *Diehr*, 450 U.S. at 189 n.12. Thus, the Federal Circuit's statement in *EMI*, if applied broadly to all claims reciting

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3. The question posed by the Petitioner also improperly merges the inquiry as to whether a claim meets the requirements of Section 112 with the issue of whether the claim is directed to an unpatentable law of nature or basic scientific principle.

laws of nature, would severely restrict the scope of patentable subject matter, contrary to the standard enunciated in *Diehr*.

When the first to recognize a law of nature obtains a patent directed to a prior art device, composition or process in combination with the newly discovered law of nature, the patent can be found invalid for anticipation under Section 102 only when the law of nature was inherently present in the prior art. The *EMI* court held that "theoretical mechanisms or rules of natural law that are recited in a claim, that themselves are not patentable . . . do not need to be recognized by one of ordinary skill in the art for a finding of inherency" because "a person of ordinary skill does not need to recognize that a method or structure behaves according to a law of nature in order to fully and effectively practice the method or structure."[4] 268 F.3d at 1351. But in a case where the newly discovered law of nature is not inherently present in the prior art, a Section 102 analysis alone will not guard against the improper monopolization of a law of nature. A separate threshold analysis under Section 101 is particularly important in this situation.

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4. *See also Schering Corp. v. Geneva Pharms., Inc.* 339 F.3d 1373 (Fed. Cir. 2003). In *Schering*, the Federal Circuit resolved a long-standing issue in its case law on the doctrine of inherent anticipation: whether recognition of the inherent feature in the prior art is required. The court held that inherent anticipation does not require that the inherent feature be appreciated by those skilled in the art at the time of the prior art patent when the feature is a necessary and inevitable consequence of the earlier invention. *Id.* at 1378.

II. THE CIRCUMSTANCES IN WHICH A SECTION 101 ANALYSIS IS APPROPRIATE SHOULD NOT BE RESTRICTED.

One of the reasons that courts may fail to conduct a threshold Section 101 analysis under *Diehr* is that it is often difficult to identify the situations in which such an analysis is required. The recital of a law of nature or a natural phenomenon as a claim element should alert a court to the need for a threshold Section 101 analysis. In determining whether the claim recites a law of nature, the court should examine how the inventor describes his invention in the written description and file history.

But it is not appropriate to restrict the circumstances in which a Section 101 analysis should be conducted because it is difficult to predict the advances in technology which may raise such concerns in the future. For example, in his concurrence in *SmithKline*, Judge Gajarsa suggested that a Section 101 analysis is necessary in a situation where a man-made composition infiltrates the natural world in such a way that it effectively alters the way that the natural world works and makes infringement essentially unavoidable. He posited the following hypothetical situation:

> Consider, for example, what might happen if the wind blew fertile, genetically modified blue corn protected by a patent, from the field of a single farmer into neighboring cornfields. The harvest from those fields would soon contain at least some patented blue corn mixed in with the traditional public domain yellow corn – thereby infringing the patent. The wind would continue to blow, and the patented crops would spread throughout the

> continent, thereby turning most (if not all) North American corn farmers into unintentional, yet inevitable, infringers. The implication – that the patent owner would be entitled to collect royalties from every farmer whose cornfields contained even a few patented blue stalks – cannot possibly be correct.

SmithKline, 403 F.3d at 1361.

Judge Gajarsa concluded that the most sensible legal reasoning for dealing with this hypothetical situation was a Section 101 analysis and that "patent claims drawn broadly enough to encompass products that spread, appear, and 'reproduce' through natural processes cover subject matter unpatentable under Section 101." *SmithKline*, 403 F.3d at 1361. We do not take any position on whether the facts presented in *SmithKline* raise an issue of patentable subject matter under Section 101, but, rather, cite the hypothetical situation presented by Judge Gajarsa as an example of the range of circumstances in which the need for a Section 101 analysis may be discerned, particularly as new technology impacts the natural world.

Accordingly, while the Court may provide some guidance on the circumstances in which a threshold Section 101 analysis is needed, we believe that it is impossible to predict all of the situations which may raise issues of patentable subject matter under Section 101 in the future.

CONCLUSION

For the above stated reasons, we see no need to modify *Diehr* and believe that a reiteration of the Court's standards for patentable subject matter as enunciated in *Diehr* will serve to place new emphasis on the essential role of a threshold Section 101 analysis with regard to patent claims that implicate laws of nature or natural phenomena.

Respectfully submitted,

CATRIONA M. COLLINS
Counsel of Record
COWAN LIEBOWITZ & LATMAN, P.C.
1133 Avenue of the Americas
New York, NY 10036-6799
(212) 790-9200

PETER A. SULLIVAN
Chair of the Committee on Patents of The Association of the Bar of the City of New York
HUGHES HUBBARD & REED LLP
One Battery Park Plaza
New York, NY 10004
(212) 837-6000

Counsel for Amicus Curiae

(26)

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Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF *AMICUS CURIAE* BOSTON PATENT LAW ASSOCIATION IN SUPPORT OF RESPONDENTS

DOREEN M. HOGLE
MEMBER, BOARD OF DIRECTORS
MEMBER, AMICUS ACTIVITIES COMMITTEE
BOSTON PATENT LAW ASSOCIATION
8 Faneuil Hall Marketplace
Boston, MA 02109
(617) 973-5021

MARK B. SOLOMON
Counsel of Record
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 Virginia Road
Concord, MA 01742
(978) 341-0036

Counsel for Amicus Curiae

199307

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INTEREST OF *AMICUS CURIAE*[1]

The Boston Patent Law Association ("BPLA") is a non-profit association of intellectual property professionals providing programs and forums for the exchange of ideas and information about patent and other intellectual property rights. The BPLA files this *amicus* brief in support of Respondents, but remains neutral as to the outcome of the case. The BPLA is concerned how the analysis of patent eligible subject matter will impact inventors and their ability to protect their intellectual property rights.

INTRODUCTION

The question presented for review by the Court is whether the method encompassed by Claim 13 of U.S. Patent 4,940,658 (hereinafter the '658 patent) is indefinite, undescribed, and non-enabling.[2] As presented, the question

1. The parties have consented to the filing of this brief *amicus curiae*. The letters of consent have been filed with the Clerk of the Court. In accordance with Supreme Court Rule 37.6, *amicus curiae* states that this brief was not authored, in whole or in part, by counsel to a party, and that no monetary contribution to the preparation or submission of this brief was made by any person or entity other than the *amicus curiae* or its counsel.

2. The question presented is

> Whether a method patent setting forth an indefinite, undescribed, and non-enabling step directing a party simply to 'correlat[e]' test results can validly claim a monopoly over a basic scientific relationship used in medical treatment such that any doctor necessarily infringes the patent merely by thinking about the relationship after looking at a test result.

begs the real issue of subject matter eligibility that is the focus of much of Petitioner's argument, and argument presented by numerous amici and commentators. Thus, the essential question presented for review is whether Claim 13, as issued, covers patentable subject matter under 35 U.S.C. § 101.[3]

It is fitting that the analysis of the patentability of Claim 13, and the resulting impact on scientific and technological progress resulting from the confirmation of its patentability, begin with the issue of statutory subject matter. Although the issue of patentability of Claim 13 during prosecution of the application before the Patent Office and subsequent review of patentability by the District Court for the District of Colorado and Court of Appeals for the Federal Circuit did not address this essential question, statutory subject matter is certainly the threshold question to be asked. For if the subject mater covered by the claim does not fall within statutory decree, then no need exists for further inquiry into the issues of definiteness, written description and enablement (as well as novelty and non-obviousness). The initial hurdle of compliance with statutory subject matter must be overcome before these subsequent limits on patentability are determined.

The analysis of patent eligible subject matter becomes much more difficult when one must further determine whether the subject matter falls within one of the judicially created exceptions to patentablity: laws of nature, natural phenomena, or abstract ideas.

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3. 35 U.S.C. § 101 reads: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."

But even after determination that the claimed subject matter is not excluded from patentability, the inquiry must go even further to address the policy concerns underlying patent eligibility. Would confirmation of the patentability of the subject matter covered by the claim at issue remove crucial knowledge from the public domain?

Our position is that the process covered by Claim 13 does encompass patentable subject matter under 35 U.S.C. § 101, and that confirming the patentability of Claim 13 will not preempt scientific knowledge from the public domain.[4]

ARGUMENT

I. When Read as a Whole, Claim 13 Encompasses Patentable Subject Matter Under 35 U.S.C. § 101

A. The Constitution and Congress Promote a Wide Range of Patent Eligible Subject Matter

Art. 1, § 8, clause 8 of the U.S. Constitution recites a sweeping directive to promote progress of useful arts by conferring exclusivity to an invention for a limited time to the inventor(s). The first U.S. Patent Acts of 1790 and 1793 defined the statutory categories of patentable subject matter as a useful art, machine, manufacture, composition of matter or any improvement therein. These categories were confirmed

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4. It is also paramount to remember that, although the analysis herein focuses on the determination of § 101 patent eligible subject matter, additional statutory and judicial constraints on patentability must also be considered. For example, the statutory requirements of 35 U.S.C. § 112 (definiteness, written description, and enablement), § 102 (novelty), and § 103 (non-obviousness) must still be met before a claim can be deemed patentable.

by the U.S. Patent Act of 1952 with a bit of modernization by changing the term "art" to "process."

The intent of the Constitution and Congress is clear. In return for an inventor's full disclosure of the invention to the public, the inventor can enjoy the recognition and economic benefits of the invention for a limited time. The "quid pro quo" is a limited time of monopoly for the dissemination of details of the invention so that one of skill in the art can understand and practice the invention. Without the grant of exclusivity for the invention, inventors would keep their technological innovations from the public, thus precluding others from learning of and improving on the technology.

Technological innovation has advanced significantly since the passing of the last Patent Act in 1952. With huge advances in science and technology leading to inventions that were only "science fiction" in 1952, Congress and the courts have had to define, refine, and impose limits on the scope of statutory subject matter while still adhering to the mission of promoting the progress of the arts and sciences. Although the courts agree that "Congress intended statutory subject matter to 'include anything under the sun that is made by man,'" *Diamond v. Diehr*, 450 U.S. 175, 182 (1981), limits have been set, and fine lines have been drawn to exclude from patent protection "laws of nature, physical phenomena and abstract ideas." *Id.* at 185. How to determine whether claimed subject matter is patent eligible or excluded has been the subject of numerous decisions. *See, e.g., Diamond v. Diehr*, 450 U.S. 175 (1981); *Diamond v. Chakrabarty*, 447 U.S. 303 (1980); *Funk Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948). These decisions have led to three categories of subject matter excluded from the scope of patent eligible

subject matter. Laws of nature (*e.g.*, $E=mc^2$), physical phenomena, and abstract ideas, such as mathematical algorithms, are not patentable. Laws of nature or scientific principles are fundamental truths outside the scope of the statute.[5]

But what if the scientific principle is not an "always-existing" fundamental truth? What if there are variations of the "truth" under certain conditions? What if it could be $E=m^2c$ under certain conditions and $E=mc^2$ under other conditions? That is, when is a "fundamental truth" not "fundamental" and thus patent eligible subject matter? It would be reasonable to propose that, when analysis is required to determine under which conditions the scientific principle applies, or when correlation of a particular condition to the scientific principle is required, the fundamental truth is no longer fundamental and is eligible for patent protection.

B. The Presence of a Law of Nature, Natural Phenomena or Abstract Idea in a Claim Does Not Automatically Exclude the Claim from the Realm of Statutory Subject Matter

The "application of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection," *Diehr*, 450 U.S at 187; *see also Parker v. Flook*, 437 U.S. 584, 590 (1978); *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972). If the claimed process results in a physical transformation for which a practical application is disclosed in the specification or

---

5. "A principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented, as no one can claim in either of them an exclusive right". *LeRoy v. Tatum*, 55 U.S. (14 How.) 156, 175 (1982); *See also Funk Brothers Seed Co.*, 333 U.S. 127, 132 (1948); *Chakrabarty*, 447 U.S. at 309.

known to one of skill in the art, or if the claimed process is limited to a practical application which produces a useful, tangible and concrete result, the claimed process encompasses statutory subject matter. *See Diehr*, 450 U.S. at 183-84 quoting *Cochrane v. Deneer*, 94 U.S. 780, 787-88 (1877). The claimed invention as a whole must accomplish a practical application and a useful, concrete, and tangible result. *State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 149 F.3d. 1368, 1374 (Fed. Cir. 1998); Manual of Patent Examining Procedure (MPEP) 2106 (II)(A) August 2005. Patentable inventions should have practical value as opposed to "subject matter that represents nothing more than an idea or concept, or is simply a starting point for future investigation or research." MPEP 2106 (II)(A) August 2005. *See also Brenner v. Manson*, 383 U.S. 519 (1966); *Arrhythmia Research Technology, Inc. v. Corazonix Corp.*, 958 F.2d 1053, 1059 (Fed. Cir. 1992); *AT&T Corp. v. Excel Communications, Inc.*, 173 F.3d 1352, 1358 (Fed. Cir. 1999); *In re Alappat*, 33 F.3d 1526, 1543 (Fed. Cir. 1994).

Admittedly, it is a difficult analysis. When does the application of a law of nature or a scientific principle satisfy the requirements of patent eligible subject matter? When does a claim containing a scientific principle transcend the line between an unpatentable claim covering the principle itself to a patentable claim that uses that principle in a process which, "when considered as a whole is performing a function which the patent laws were designed to protect?" *Diehr*, 450 U.S. at 192. The focus must be on whether there is a transformation from mere statement of principle to useful result.

It is also well-established law that assessment of patentability of a claim must evaluate the claim as a whole.

> In determining the eligibility of respondents' claimed process for patent protection under 101, their claims must be considered as a whole. It is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis. This is particularly true in a process claim because a new combination of steps in a process may be patentable even though all the constituents of the combination were well known and in common use before the combination was made.

Diehr, 450 U.S. at 188-89.

Moreover, not only the active steps of the process can be considered in the analysis. If the preamble "breathes life and meaning into the claim" and limits the claimed invention, then the preamble must be treated as a claim limitation.[6] In determining whether an inventor seeks patent protection for a bare scientific principle, or a useful application of that principle, the claim as a whole, at times including the limitations of the preamble, must be considered.

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6. The preamble of a claim directed to a method of treating or preventing anemia by administering certain vitamin preparations to a human "in need thereof" was not "merely a statement of effect that may or may not be desired or appreciated, but rather is a statement of the intentional purpose for which the method must be performed." MPEP 2111.02(II) quoting *Jansen v. Rexall Sundown, Inc.*, 342 F.3d. 1329, 1333-34 (Fed. Cir. 2003).

C. When Read as a Whole, Claim 13 Encompasses Patentable Subject Matter

Claim 13 reads:

> A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> Assaying a body fluid for an elevated level of total homocysteine; and
>
> Correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

During prosecution of the application before the United States Patent Office, the Patent Examiner required the "correlating" phrase to be included in the claim so that the step of assaying a body fluid is clearly related to the preamble. The preamble of Claim 13 is to be given "meaning," whereby the claimed steps of assaying and correlating are performed to detect, if present, a deficiency of cobalamin or folate in a subject. Clearly the Patent Office believed that the purpose of the process, to detect a deficiency of cobalamin or folate, gave meaning to the claim and should not be discounted in the analysis of patentable subject matter. Thus, when read "as a whole," the claimed invention encompasses (as paraphrased into a more conversational recitation):

> A process for detecting a B vitamin deficiency in a subject by analyzing a body fluid obtained from the subject by performing a homocysteine assay to determine the amount of homocysteine in the

body fluid and relating the levels of homocysteine in the body fluid to a determination of whether or not there is a B vitamin deficiency.

When read as a whole, does this claim cover a scientific principle? Is it a fundamental truth that every time there is an elevated homocysteine level in a blood sample the subject suffers from a B vitamin deficiency? An elevated level of total homocysteine can result from other causes and is not necessarily the consequence of a vitamin deficiency. For example, a genetic defect exists – homocysteinuria – which leads to high levels of homocysteine in the blood or urine (body fluids as recited in Claim 13) of subjects suffering from this disease.[7] Therefore, it is not a fundamental truth that elevated levels of homocysteine in a body fluid always means a deficiency of a B vitamin. An elevated level of homocysteine can also be correlated to a genetic disease, not a B vitamin deficiency. In view of such analysis, one should recognize that the claimed process is not synonymous with the existence of any basic scientific relationship between the assay result and the condition of the subject.

However, even if one were to assume that the relationship between homocysteine levels and vitamin deficiency is a fundamental truth, i.e., elevated homocysteine always means

---

7. Homocysteinuria is an inherited disorder of the metabolism of the amino acid methionine. (*See* the National Institutes of Health, July 26, 2004 *http://www.mlm.nih.gov/medlineplus/ency/article/001199.html*.) Homocysteinuria is a genetic disorder in which blood and urine levels of homocysteine, a metabolite of the amino acid methionine, are significantly higher than the normal concentration. The genetic defect lies in an enzyme, cystathionine b-synthetase, which generates a substance called cystathionine from homocysteine. National Organization for Rare Diseases *http://www.rarediseases.org*).

a B vitamin deficiency, Claim 13 is not excluded from patentability based on the claimed subject matter. Just because a process claim includes a scientific principle, it does not necessarily follow that the process claim is outside the scope of statutory subject matter under 35 U.S.C. § 101. If the claim produces a practical result, it can still fall within the scope of patentable subject matter notwithstanding the recitation of a scientific principle.

In *Diehr*, the Court held that a claim for a process for curing rubber that included a mathematical algorithm encompassed statutory subject matter because use of the algorithm produced a practical result. *Diehr*, 450 U.S. at 186-187. Following the decision in *Diehr* and a long line of supporting Court decisions, the United States Patent and Trademark Office recently issued interim guidelines for examination of patent applications for subject matter eligibility. Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility October 26, 2005, published in the Official Gazette November 22, 2005, *http://www.uspto.gov/web/offices/com/sol/og/2005/week47/patgupa.htm*, hereinafter "Guidelines".

The Guidelines set forth two alternative criteria for determining whether a claim that contains a law of nature/scientific principle satisfies the requirements for patent eligible subject matter. Does the claimed invention "transform" an article or physical object to a different state or thing, or does the claimed invention otherwise produce a useful, concrete, and tangible result? Guidelines at 19; *AT&T Corp. v. Excel Communications, Inc.*, 172 F.3d 1352 (Fed. Cir. 1999); *State Street Bank & Trust Co. v. Signature Financial Group, Inc.*, 149 F.2d 1368 (Fed. Cir. 1998).

> In determining whether a claim is for a 'practical application', the focus is not on whether the steps taken to achieve a particular result are useful, tangible and concrete, but rather that the final result achieved by the claimed invention is 'useful, tangible and concrete'."

Guidelines at 20; *AT&T Corp.*, 172 F.3d 1352 (Fed. Cir. 1999); *State Street Bank*, 149 F.2d 1368 (Fed. Cir. 1998); *In Re Alappat*, 33 F.3d 1526 (1994).

In *Arrhythmia Research Technology, Inc. v. Corazonix Corp.*, 958 F.2d 1053, the court held that a method to analyze heartbeat falls within the confines of statutory subject matter. The process analyzed electrical signals from a patient's heart by converting the signal into a value and then comparing that value to a predetermined value to predict vulnerability to ventricular tachycardia immediately after heart attack. This process of analysis of heart activity transformed the heart's electrical activity into a useful result – the condition of the patient's heart. "[T]he '459 patent as a whole does not present a mathematical algorithm. The '459 patent is a method for detecting the risk of a heart attack, not the presentation and proposed solution of a mathematical problem." *Arrhythmia*, 958 F.2d. at 1066, Rader, J. concurring opinion, citing *Diehr*, 450 U.S. at 186.

> *Diehr* refocused the patentability inquiry on the terms of the Patent Act rather than on non-statutory, vague classifications. Under the terms of the Act, a 'process' deserves patent protection if it satisfies the Act's requirements.

Id. at 1066.

So too in the disputed Claim 13, the process assays/analyzes the homocysteine molecules in a body fluid and transforms that signal/data to detect a B vitamin deficiency. Accordingly, when read as a whole, Claim 13 is a process that satisfies the requirements of 101 and deserves patent protection.

Whereas the *Arrythmia* case involved the use of a machine, the Court of Appeals for the Federal Circuit has ruled that it is of little relevance whether a claim is directed to a machine or process for a 101 analysis. Claims do not fall outside of the realm of non-statutory subject matter merely because some or all of the steps are carried out by a human mind or involve thought processes. *In re Musgrave*, 431 F.2d 882, 892 (CCPA 1970). "If all the steps of a claimed process can be carried out in the human mind, examiners must determine whether the claimed process produces a useful, tangible and concrete result, i.e., apply the practical application test set forth in *State Street*." Guidelines at 47. The process steps of Claim 13 produce a concrete tangible and useful result of the homocysteine assay – the detection of a vitamin deficiency. Thus, Claim 13, when read as a whole, encompasses statutory subject matter.

II. Confirming the Patentability of Claim 13 Would Not Preempt the Use of a Scientific Principle by Others

One must ensure, however, that when a law of nature, mathematical algorithm or abstract idea is part of a seemingly patentable process that, in reality, the law of nature, algorithm or idea does not preempt the use of that law, algorithm or idea to foreclose other uses. "A principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented, as no one can claim in either of them an exclusive right." *Funk Brothers Seed Co.*, 333 U.S. 127, 132 (1948);

see also Diehr, 450 U.S. at 191. Knowledge once in the public domain must remain in the public domain. *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 484 (1970).

A. Claim 13 Does Not Remove the Existence of Knowledge from the Public Domain

As stated in *Diehr*,

> In contrast, the respondents here do not seek to patent a mathematical formula. Instead, they seek patent protection for a process of curing synthetic rubber. Their process admittedly employs a well-known mathematical equation, but they do not seek to pre-empt the use of that equation. Rather they seek only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process.

Diehr, 450 U.S. at 187.

The analogy to *Diehr* is convincing. The inventors of Claim 13 do not seek to patent a scientific principle. They seek to patent a process for detecting a B vitamin deficiency. Claim 13, when read as a whole, covers a method of detecting a cobalamin or folate deficiency by assaying and analyzing homocysteine in a body fluid. As discussed above, elevated homocysteine levels can indicate a vitamin deficiency or a genetic defect. Correlating the homocysteine assay results to a vitamin deficiency, as opposed to a genetic defect, is a practical application of assaying homocysteine levels.

Would confirming the patentability of Claim 13 remove the existence of the knowledge from the public domain? No. In their patent application, patentees disclosed to the world the invention that assaying homocysteine is predictive

of a vitamin B12 or folate deficiency in a human. Patentees have not removed information from the public domain, but added to the public knowledge by disclosing a practical assay for the detection of cobalamin and folate deficiencies in humans. Prior to patentees' disclosure such a method was not known.

Moreover, information on cobalamin and folate deficiencies is still readily available. Scientific journals are not prohibited from publishing studies on vitamin deficiencies. Dissemination of critical medical information is still possible. Doctors and medical researchers are free to discuss and elaborate on the implications of homocysteine levels and vitamin deficiencies, or heart disease or genetic disease. No restriction on the dissemination of such medical information is precluded by confirming the patentability of Claim 13.

B. The Effects of Patenting a Medical Process Are No Different From Patenting a Medical Device

The quid pro quo for disclosing their invention to the world is that patentees now hold the legal right to exclude others from practicing their invention. Although legally permissible, in practice, common sense dictates that patentees cannot enforce their rights against every infringer. However, Diehr *can* exclude others from curing rubber using the patented process. State Street Bank *can* exclude others from practicing their patented method of investment configuration. Arrhythmia Research Technology *can* exclude others from using their patented electrocardiograph device from detecting heart irregularities. By confirming the patentability of Claim 13 the Court confirms the legal right of Respondents to exclude others from practicing their patented process of detecting a B vitamin deficiency.

Perhaps it is easier to appreciate exclusivity conferred on a machine or a device because it is a tangible object. Recently issued medical device patents include patents for artificial heart valves (*e.g.*, U.S Patent 6,991,649); coated medical devices (*e.g.*, U.S. Patent 6,921,811); artificial limbs (*e.g.*, U. S. Patent 6,936,073); and orthopedic splints (*e.g.*, U.S. Patent 6, 991,612). These medical devices are also premised on scientific principles. The functionality of an artificial heart valve is based on the scientific principles of fluid dynamics. Artificial limbs are based on the scientific principles of mechanical dynamics. Yet a patentee who patents a life-saving artificial heart valve or an artificial limb is granted a limited monopoly on their invention without question of pre-emption of a scientific principle. No distinction should be imposed because the subject matter is a medical process. The patent laws clearly include processes within the realm of patentable subject matter. Exclusivity conferred on a patented medical process should be treated no differently from the exclusivity conferred on patented medical devices.

C. The Intent of the Constitution and Congress is Safeguarded

The intent of the Constitution is to promote the progress of science and the useful arts. This directive has been supported by Congress and upheld by case law. Claim 13 confers on patentees a limited monopoly for a method of detecting a vitamin deficiency in a human by assaying homocysteine levels. Disclosure of this method has clearly advanced the knowledge of medical technology, for a reliable test for detecting B vitamin deficiencies in a human by analyzing levels of homocysteine was not previously known.

But, just because the patentees discovered a method of detecting a vitamin deficiency that is the current "state-of-the-art," it does not mean that others cannot improve on the method. In the future, someone may discover another method of detecting vitamin deficiencies that supplants the method of Claim 13, and that latter methods will become "state-of-the-art." Scientific research is not stagnant, and innovative advances are built on the knowledge of others. If there is a medical problem to be solved, someone will invent a solution. The competitive spirit will persist despite a patent being granted on a medical process or device. As we all know, designing around a patent is a well-recognized, and legal, exercise of technological innovation. The claimed process may confer exclusive rights on the patentees, but other researchers will continue in their quest to improve the technology.

But how will these "design-around" innovations be invented? Who will pay for the research? Are there only altruistic motives driving medical discovery? A significant driving force behind innovation and invention is financial reward. Medical researchers compete for limited amounts of research dollars to continue their research, relying heavily on their previous successes. Government grant applications request lists of patents as well as scientific publications. Medical institutions use patent license revenues to supplement government grant money designated for research. Technology-based companies, whether large or small, also rely on patented inventions to attract investor funding for growth. The rewards that stem from patented technology are critical components of the forces that drive innovation. Our forefathers recognized this when they conveyed the right of a limited monopoly to an inventor so that inventors could reap the rewards of their innovative achievements. Thus, confirming the patentability of Claim 13 will not hinder innovation, and the public will continue to be served by scientific and technological progress.

CONCLUSION

Respondent's method of correlating an elevated level of total homocysteine in the body fluid of a warm-blooded animal with a deficiency of cobalamin or folate is patent eligible subject matter. Correlating test results, as prescribed by Claim 13, does not impose a monopoly over a basic scientific relationship used in medical treatment. Any doctor looking at a test result of an assay suitable for complying with the assaying step of Claim 13 does not infringe the patent merely by thinking about a relationship between an elevated level of total homocysteine and a deficiency of cobalamin or folate. The monopoly conferred by a valid method patent, which is based on discovery of a basic scientific relationship, extends only to those who conduct a test for the purpose of correlating the test result with a condition associated with the relationship.

Where the test is known in the art, the application of the test is a limitation on the use of the test, just as discovery of a new use for a known device, likely also based on a "basic scientific relationship," is a limitation on the use of the device. In both cases, the monopoly does not exclude others from using the basic scientific relationship, only the claimed method.

We believe that Claim 13, when read as a whole, encompasses statutory subject matter under 35 U.S.C. § 101 as envisioned by the Constitution and Congress, and as supported by the Courts. We further believe that confirming the patentability of Claim 13 would not preempt the use of a scientific principle or remove the existence of knowledge from the public domain.

Respectfully submitted,

DOREEN M. HOGLE
MEMBER, BOARD OF DIRECTORS
MEMBER, AMICUS ACTIVITIES COMMITTEE
BOSTON PATENT LAW ASSOCIATION
8 Faneuil Hall Marketplace
Boston, MA 02109
(617) 973-5021

MARK B. SOLOMON
Counsel of Record
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 Virginia Road
Concord, MA 01742
(978) 341-0036

Counsel for Amicus Curiae

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LABORATORY CORPORATION OF AMERICA HOLDINGS (D/B/A LABCORP),

Petitioner,

v.

METABOLITE LABORATORIES, INC., ET AL.,

Respondents.

On Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

BRIEF FOR *AMICUS CURIAE* COMPUTER & COMMUNICATIONS INDUSTRY ASSOCIATION IN SUPPORT OF PETITIONER

BRIAN KAHIN
MATTHEW SCHRUERS
COMPUTER & COMMUNICATIONS INDUSTRY ASSOCIATION
666 Eleventh Street, NW
Washington, DC 20001
(202) 783-0070

JONATHAN BAND
Counsel of Record
JONATHAN BAND PLLC
21 Dupont Circle NW
8th Floor
Washington, DC 20036
(202) 296-5675
jband@policybandwidth.com

Counsel for Amicus Curiae

December 23, 2005

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OR CALL COLLECT (402) 342-2831

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BRIEF FOR *AMICUS CURIAE* COMPUTER & COMMUNICATIONS INDUSTRY ASSOCIATION IN SUPPORT OF PETITIONER

The Computer & Communications Industry Association (CCIA) submits this brief as *amicus curiae* and respectfully requests that the Federal Circuit be reversed. Petitioner and Respondents have consented to the filing of this brief, and the letters of consent are being filed herewith.

INTEREST OF *AMICUS*

The Computer & Communications Industry Association is a non-profit trade association dedicated to open markets, open systems, and open networks. CCIA members participate in many sectors of the computer, information technology, and telecommunications industries and range in size from small entrepreneurial firms to the largest in the industry.[1] CCIA members use the patent system regularly, and depend upon it to fulfill its constitutional purpose of promoting innovation. CCIA is increasingly concerned that the patent system has expanded without adequate accountability and oversight.[2]

CCIA supports the Petitioner's argument for reversal of the Federal Circuit. This brief addresses how the

[1] Counsel for a party did not author this brief in whole or in part. No person or entity other than CCIA, its members, or its counsel made a monetary contribution to the preparation or submission of this brief.

[2] CCIA is a trade association with a wide and diverse membership. It was unable to resolve the reservation of one of its members, Verizon Communications, prior to the filing of this brief. These views should therefore not be associated with Verizon.

Federal Circuit has inappropriately enlarged the scope of patentable subject matter, without foundation and in contradiction to this Court's precedent. The brief argues that to restore order this Court must reaffirm the principles expressed in *Cochrane v. Deener*, 94 U.S. 780 (1876), and *Diamond v. Diehr*, 450 U.S. 175 (1981): that in order to be patentable, a process must result in a physical transformation.

Neither CCIA nor its members have a direct financial interest in the outcome of this litigation. However, allowing the Federal Circuit's interpretation of the scope of patentable subject matter to stand would subject CCIA members to increased patent litigation, burden information technology and software, and undermine the legitimacy of the patent system as a whole.

SUMMARY OF THE ARGUMENT

As this Court's February 28 order to the Solicitor General suggests, the Federal Circuit's interpretation of the scope of patentability as formulated in *State Street Bank & Trust Co. v. Signal Financial Group, Inc.*, 149 F.3d 1368, 1373 (Fed. Cir. 1998), *cert. denied*, 119 S. Ct. 851 (1999), has ventured far beyond this Court's precedents, including *Diamond v. Diehr*. *See* Feb. 28 Order, 125 S. Ct. 1413.[3] This brief describes the problems created by a lack of meaningful limits on patentable subject matter, demonstrated most clearly by the problem of so-called "business method" patents.

[3] This inquiry is fairly included within the question presented, a fact noted by Petitioner in its supplemental brief. Suppl. Pet. Br. at 5.

This case squarely presents the central issue of patent policy in today's knowledge-driven economy: drawing the line between abstract idea and patentable process. With the explosive success of the Internet and the World Wide Web enabling a wealth of new business models, this question becomes as critical and challenging as delineating expression from idea in copyright. It is as important for software and services as it is for biotechnology and medical practice; this question must be answered for all innovation environments.

The answer to this question must be unequivocal: the Court must reaffirm its definition of "process," first articulated in *Cochrane v. Deener*: "A process is a mode of treatment of certain materials to produce a given result. It is an act, or a series of acts, performed upon the subject-matter to be transformed and reduced to a different state or thing. If new and useful, it is just as patentable as is a piece of machinery." 94 U.S. 780, 788 (1876). This definition was reaffirmed by the choice of "process" as one of the categories of patentable subject in the Patent Act of 1952 and by the Court in *Diamond v. Diehr*, 450 U.S. 175, 182-84 (1981).

This brief argues that the Federal Circuit's expansion of patentable subject matter disregards this Court's precedents and lacks statutory basis. Rather than relying on statute or this Court's opinions, *State Street* invokes vague legislative history in the form of committee reports to justify expanding limits on patentable subject matter in Section 101 of the Patent Act. Even then, the legislative history proves to be too thin a reed to justify the conclusions reached in *State Street*. Having thus justified its expansion of patentable subject matter, the Federal Circuit crafted a new test that lacks statutory basis and has effectively supplanted this Court's standard first

articulated in *Cochrane v. Deener*. This judicial enlargement of the subject matter limitations of Section 101 has radically broadened the Patent Act into a general law of novelty, distorting the Act's statutory foundation and in some cases failing its constitutional purpose. U.S. Const. art. 1, § 8, cl. 8.

This brief concludes that reassertion of the *Cochrane* standard is necessary to remedy the dysfunctional system that the Federal Circuit has created: one which encourages opportunism while undermining innovation, leaving governments worldwide struggling with the results.

Correcting the Federal Circuit's misconstruction of Section 101 will contribute to the restoration of order and restraint in our troubled patent system. Accordingly, CCIA respectfully requests that the Court reverse the ruling below and meaningfully enforce limitations of the scope of patentable subject matter.[4]

ARGUMENT

I. THE FEDERAL CIRCUIT'S EXPANSION OF PATENTABLE SUBJECT MATTER DISREGARDS THIS COURT'S PRECEDENTS AND LACKS STATUTORY BASIS.

The question posed by the Court to the Solicitor General was whether the process claimed by respondent Metabolite is statutory subject matter under *Diamond v.*

[4] It is unquestionable that business methods, like the diagnostic correlation in this case, produce no transformation, and are therefore unpatentable. Thus, "line-drawing" with respect to the patentability of other subject matter, including software, is unnecessary.

Diehr. Writ large, this question highlights the problem created by the Federal Circuit's unsanctioned enlargement of the statutory scope of patentability. This case offers a vehicle for correcting that problem.

Diehr was the last of a well-known trio of cases, including *Gottschalk v. Benson*, 409 U.S. 63 (1972), and *Parker v. Flook*, 437 U.S. 584 (1978), in which the Court established the scope of patentable subject matter. In *Benson*, the court explained that "[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." 409 U.S. at 67.

Since *Diehr*, the Supreme Court has not revisited the line between patentable processes and abstract ideas. Yet in the interim, the Court of Appeals for the Federal Circuit has aggressively expanded the scope of the patent system to cover areas of knowledge intended neither by this Court nor by Congress. *See, e.g., In re Alappat*, 33 F.3d 1526 (Fed. Cir. 1994); *State Street Bank & Trust Co. v. Signal Financial Group, Inc.*, 149 F.3d 1368, 1373 (Fed. Cir. 1998), *cert. denied*, 119 S. Ct. 851 (1999); *AT&T Corp. v. Excel Communications, Inc.*, 172 F.3d 1352 (Fed. Cir. 1999). Despite the lack of evidence that Congress intended this enlargement – and in the face of evidence to the contrary – the Federal Circuit's expansionism swept away preexisting jurisprudential limitations. These limitations, including mental steps, function of a machine, and methods of doing business, had helped innovators navigate the line between patentable and unpatentable. *See, e.g., In re Musgrave*, 431 F.2d 882 (C.C.P.A. 1970); *In re Tarczy-Hornoch*, 397 F.2d 856, 866-67 (C.C.P.A. 1968); and *State Street Bank & Trust Co., supra*.

State Street both sidestepped this Court's holdings in *Benson*, *Flook*, and *Diehr*, and usurped the policymaking role of the Congress. It reversed hornbook law upon which businesses and lawyers relied. It ignored this Court's definition of process articulated first in *Cochrane v. Deener* and on which the decision in *Diehr* was predicated. *See* 450 U.S. at 183-84. Instead, *State Street* reread the 1952 Patent Act as overturning a longstanding judicial rule against patents for methods of doing business. It did not offer any direct evidence of such intent, because there is none. Rather, *State Street* claimed to have found intent by Congress to abandon traditional subject matter limitations in a formerly obscure clause of legislative history, the now infamous mantra, "anything under the sun that is made by man." In place of long-established standards, *State Street* plucked a new standard – a "useful, concrete and tangible result" – from a sentence that the Federal Circuit itself had written four years earlier. *See State Street*, 149 F.3d at 1373 (quoting *Alappat*, 33 F.3d at 1544).

A. Vague Legislative History Provides the Sole Justification for the Federal Circuit's Expansion of Section 101's Limits on Patentable Subject Matter.

Since the Patent Act was passed in 1952, the Federal Circuit (along with its predecessor, the Court of Customs and Patent Appeals) has radically expanded the scope of patentable subject matter by redrawing the line between patentable processes and abstract ideas. This expansion, most conspicuously manifest in the area of business method patents, has been justified by the judicial bootstrapping of a reference in a committee report in the

legislative history to "anything under the sun that is made by man."

1. State Street's *Mantra Derives Solely From Committee Reports*

The phrase "anything under the sun that is made by man" first appeared in House and Senate committee reports on the Patent Act, which were drafted by a Patent Office employee.[5] *See* S. Rep. No. 1979, 82d Cong., 2d Sess., at 5 (1952); H. R. Rep. No. 1923, 82d Cong., 2d Sess., at 6 (1952). The phrase is an offhanded dependent clause in a sentence that reads: "A person may have 'invented' a machine or a manufacture, which may include anything under the sun that is made by man, but it is not necessarily patentable under Section 101 unless the conditions of the title are fulfilled." The sentence as a whole is not directed at the scope of patentable subject matter, but rather at the requirements of patentability. In other words, the sentence states that even if a person invented a machine, it is only patentable if it meets all the other requirements of the Act. Moreover, the phrase "anything under the sun that is made by man" modifies the words "a machine or a manufacture," and thus does not refer to *processes*.

This phrase lay dormant for nearly thirty years, until Judge Giles Rich, one of the principal authors of the Act, quoted it in his three-stage formula for how to read the basic requirements of the Patent Act. *See In re Bergy*, 596

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[5] *See* Giles S. Rich, *Congressional Intent – Or, Who Wrote the Patent Act of 1952* reprinted in *Patent Procurement and Exploitation* 73 (BNA 1963).

F.2d 952, 987 (C.C.P.A. 1979); *see also* A. Samuel Oddi, *Assault on the Citadel: Judge Rich and Computer-Related Inventions*, 39 Houston L. Rev. 1034, 1074-76 (2002) (recounting history of phrase). This Court affirmed *Bergy* in *Diamond v. Chakrabarty*, with Justice Burger repeating in dicta the "anything under the sun" phrase devoid of its context. 447 U.S. 303, 309 & n.6 (1980).

The following year in *Diamond v. Diehr*, the Court again recited in dicta that "Congress intended statutory subject matter to 'include anything under the sun that is made by man.'" 450 U.S. 175, 182 (1981). *Diehr* uses the phrase, again out of context, to refer to a process rather than a machine or manufacture as the sentence requires. Most importantly, however, *Diehr* uses the phrase only to refer to traditionally patentable physical processes that, following *Cochrane v. Deener*, transform the state or nature of matter – in this case, the curing of rubber. The phrase does not, as is sometimes erroneously assumed, refer to the operation of a computer program.

Nonetheless, these dicta provided for a monumental expansion of patentable subject matter by the Federal Circuit in its controversial *State Street* decision. Judge Rich, now sitting on the Federal Circuit, seized on "anything under the sun that is made by man" out of context to strike down the longstanding rule against patents on business methods and read business methods into Section 101's explicit categories of "process, machine, manufacture or composition of matter." *State Street Bank & Trust Co. v. Signal Financial Group, Inc.*, 149 F.3d 1368, 1373 (Fed. Cir. 1998), *cert. denied*, 119 S. Ct. 851 (1999).

2. Chakrabarty *Does Not Support* State Street's *Analysis*

State Street justifies this revisionism by citing Chief Justice Burger's recitation out of context of "anything under the sun that is made by man" when finding artificial life forms patentable in *Chakrabarty*, and by citing the phrase's subsequent use in *Diehr*, where it applies to a traditional process. *See State Street*, 149 F.3d at 1373. *Chakrabarty*, however, cannot support the Federal Circuit's revisionist reading of Section 101; artificial life forms may be new and different but there is nothing abstract about them. 447 U.S. at 309. Indeed, the contrast between *Chakrabarty* and the Federal Circuit's embrace of patents on business methods could not be more stark. *Chakrabarty* involved a new kind of technology that Congress admittedly could not have foreseen in 1952, a technology solidly rooted in the natural sciences, and a technology that requires large, high-risk investments. "Methods of doing business," by contrast, are not technology at all: they are not within the "useful arts" as interpreted by *In re Musgrave*, 431 F.2d 882, 893 (C.C.P.A. 1970). Methods of doing business were neither new nor unanticipated. They had existed unprotected by patents for hundreds of years when Congress enacted the 1952 Patent Act. *See, e.g.*, *Hotel Security Checking Co. v. Lorraine Co.*, 160 F. 467, 469 (2d Cir. 1908); *Loew's Drive-In Theatres v. Park-In Theatres*, 174 F.2d 547, 552 (1st Cir. 1949) ("a system for the transaction of business . . . however novel, useful, or commercially successful is not patentable apart from the means

for making the system practically useful, or carrying it out"); *In re Patton*, 127 F.2d 324, 327 (C.C.P.A. 1942).[6]

If Congress intended to change the established rule in this regard, it was quite capable of doing so explicitly. Because the Patent Act was enacted against a backdrop of established judicial limitations on patentability, Section 101 demonstrates Congress's unwillingness to modify the scope of patentable patent subject matter. The Act's failure to reverse preexisting case law prohibiting business methods is conclusive.

3. *The Patent Act's Legislative History Fails to Support* State Street

Even assuming that Section 101 were ambiguous, legislative history cannot be read to narrow Section 101 unless that intent is "clearly expressed." *Reves v. Ernst & Young*, 507 U.S. 170, 177 (1993). As Judge Rich himself

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[6] *State Street* purports to distinguish *Hotel Security Checking* and *Loew's Drive-In* on the basis that they refused patentability on the basis of inventiveness, but these distinctions are unavailing. Both cases establish that a business method constituted an unpatentable abstract idea. *Hotel Security Checking* did not dispose of the case on lack of novelty, as *State Street* suggests. *Id.* at 1373. Although the defense asserted in *Hotel Security Checking* was lack of novelty and invention, the court disposed of the claim for lack of "*patentable* novelty," *id.* at 472, because "[n]o mere abstraction, no idea, however brilliant, can be the subject of a patent irrespective of the means designed to give it effect." *Id.* at 469. In any event, as *State Street* concedes, *Patton* is unmistakably clear that "a system of transacting business, apart from the means for carrying out such system, is not within the purview of section 4886, *supra*, nor is an abstract idea or theory, regardless of its importance or the ingenuity with which it was conceived, apart from the means for carrying such idea or theory into effect, patentable subject matter." *Id.* at 327-28.

observed, "members of the Congress wrote only a few words of the Patent Act . . . The Patent Act was written basically, however, by patent lawyers drawn from the Patent Office, from industry, from private practice, and from some government departments." Giles S. Rich, *Congressional Intent – Or, Who Wrote the Patent Act of 1952* reprinted in *Patent Procurement and Exploitation* 73 (BNA 1963). "A good 95% of the members of both bodies [of Congress] never knew that the legislation was under consideration, or that it had passed, let alone what it contained . . . How can the House, as a legislative body, be said to have any 'intent' with respect to the bill?" *Id.* at 75 (quoting Rep. Crumpacker). To then suggest that a report written by a Patent Office employee before the Act was passed reflects that intent offends common sense.[7]

Since the "anything under the sun" phrase is not even addressed to the scope of patentability, it cannot suggest that Congress intended to change the scope of patentable subject matter. In fact, there is not a word anywhere in the text or legislation to suggest that Congress intended to expand the reach of the patent system. In a colloquy on the floor of Senate, the act was represented to merely "codif[y] the present patent laws." 98 Cong. Rec. 9323 (1952). The statement inserted in the record by the sponsoring senator states it clearly in its opening line, "This legislation is another step in codification of the United

[7] "The foregoing will, it is hoped, cause you to pause and think when you hear or use the phrase 'intent of Congress.' Realistically, the 'intent,' with respect to the Patent Act of 1952, was the intent of a subcommittee to pass the bill prepared by the patent lawyers. . . . You need only compare the bill prepared by the Coordinating Committee with the law as enacted to see this." Rich, *supra*, at 77.

States Code and will enact into law title 35 of the United States." *Id.*

The absence of any such intent to expand patentable subject matter was clearly evident to Judge Rich when he wrote on the scope of patentability a mere eight years after the passage of the Act. Not only did he distinguish between patentable and unpatentable inventions, but his examples for the latter includes methods of doing business:

> Of course, not every kind of an invention can be patented. Invaluable though it may be to individuals, the public, and national defense, the invention of a more effective organization of the materials in, and the techniques of teaching a course in physics, chemistry or Russian is not a patentable invention . . . Also outside that group is one of the greatest inventions of our times, the diaper service.

Giles S. Rich, *Principles of Patentability*, 28 Geo. Wash. L. Rev. 393, 394 (1960). Under the expansive view of the patent system that *State Street* attributed to the Congress of 45 years before, these examples would be patentable.

B. "Useful, Concrete, and Tangible" Lacks Statutory Basis and Has Supplanted the "Transformation" Test.

Having justified its expansion of Section 101 with "anything under the sun," the Federal Circuit announced a standard that effectively supplants this Court's holding in *Cochrane*. *Compare State Street*, 149 F.3d at 1373, *with Cochrane*, 94 U.S. at 788. Rather than deferring to the *Cochrane* requirement of "transformation" in process

patents, the Federal Circuit cites new language from one of its own recent decisions, *In re Alappat*: "This is not a disembodied mathematical concept which may be characterized as an 'abstract idea,' but rather a specific machine to produce a useful, concrete, and tangible result." 33 F.3d 1526, 1544 (Fed. Cir. 1994). *Alappat* offers no definition of these terms. Four years later in *State Street*, the Federal Circuit elevated these terms as the new standard of patentability, again without definition.

Without explaining the fate of *Cochrane*, the Federal Circuit has introduced a standard that simply reiterates the Section 101 utility requirement and then introduces two altogether new and undefined terms, "concrete" and "tangible." It has yet to find any useful subject matter excluded by this standard.

II. REASSERTION OF THE *COCHRANE* STANDARD IS NECESSARY AS EXPANSION OF PATENTABLE SUBJECT MATTER HAS PROVED UNWORKABLE.

A. Expanding the Scope of Patentability Has Encouraged Opportunism Without Encouraging Innovation.

This Court fully understood the policy significance of extending patent protection into the realm of abstract subject matter when it first examined computer programs. The concluding paragraphs in *Benson* recognize the economic significance of the problem and the very limited capacity of courts to address it:

> It may be that the patent laws should be extended to cover these programs, a policy matter to which we are not competent to speak. . . . If

> these programs are to be patentable, considerable problems are raised which only committees of Congress can manage, for broad powers of investigation are needed, including hearings which canvass the wide variety of views which those operating in this field entertain. The technological problems tendered in the many briefs before us indicate to us that considered action by the Congress is needed.

Benson, 409 U.S. at 72-73. *Compare with Diehr*, 450 U.S. at 184-87 (concluding, after extended consideration, that subject matter does not become nonstatutory merely due to usage of a computer). The measured analysis that this Court has required before expanding the scope of patentable subject matter is absent from *State Street*.

By removing widely understood barriers to patentable subject matter, *State Street* validated the concerns voiced in *Benson*, and proved a case study in the dangers of creating new rights overnight. The extraordinary breadth offered by patents on business methods sparked an instant land rush.[6] Ironically, this was fueled by the extraordinary success of the *nonproprietary* platforms of the Internet and the World Wide Web, upon which anyone could build freely. Entrepreneurs scrambled to patent the first Internet-based implementation of known processes, such as reverse auctions, because the Federal Circuit's low nonobviousness standard for combinations of known art made

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[6] So serious was the problem of questionable "Electronic Commerce" patents (Class 705) that the PTO launched a special initiative in order to reduce the allowance rate from a staggering 75 percent. *See* David Streitfeld, *Note: This Headline is Patented*, L.A. Times, Feb. 7, 2003, at A1.

such patents easy to get. *See* U.S. Patent No. 5,794,207 (issued Aug. 11, 1998) (reverse auctions on the Internet).[9]

This deadly combination along with other Federal Circuit rulings that have raised the presumption of validity and made injunctive relief automatic have fueled an economic and institutional addiction to a high volume of patenting. When the Federal Circuit decided *State Street*, no one was advocating patents on business methods. *State Street* created an instant constituency for such patents, not only among those rushing to secure them, but also among the community of patent professionals, who stood to benefit greatly from the expanded business. *State Street* helped create a sellers' market for patent-related legal services, in which professional fees rose approximately 50% over the four years from 1999 to 2003.[10] Once this highly motivated constituency was created, it proved too difficult for Congress to undertake the arduous task of undoing the Federal Circuit's errors.

Unlike patents for technologies, the broad, sweeping nature of many business method patents, such as the infamous one-click ordering patent, drew hordes of would-be monopolists. The Undersecretary for Intellectual Property and Director of the Patent and Trademark Office even expressed support for patents on novel and nonobviousness legal arguments.[11] However, such patents also

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[9] The problems created by questionable combination patents is presented to this Court in the petition in *KSR International v. Teleflex, Inc.*, 04-1350.

[10] AIPLA, Report of the Economic Survey 1999, 2001, and 2003.

[11] Steven Pizzo, *Who's Really Being Protected?* O'Reilly Network, May 24, 2000, at 3, *available at* <http://www.oreillynet.com/pub/a/policy/2000/05/24/PizzoFiles.html>.

drew unprecedented public attention and often condemnation, in part because their nontechnical nature made them easy for the public to grasp.[12] Ironically, patents at this level of abstraction actually discourage technological innovation by preempting competition among different implementations. As IBM observed:

> [W]ith the advent of business method patenting it is possible to obtain exclusive rights over a general business model, which can include ALL solutions to a business problem, simply by articulating the problem. No investment in research and development needed to create an actual, practical, workable solution to the problem is required.[13]

Yet rather than acknowledge the problems associated with granting nontraditional patents on intangible subject matter, the patent community has cast the particular problems as failures of the examination process, the answer to which is not to cut back on subject matter but to provide greater resources to the agency.

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[12] *See* U.S. Patent No. 5,960,411 (issued Sept. 28, 1999) (one-click); U.S. Patent No. 6,329,919 (issued Dec. 11, 2001) (system for toilet reservations); *see also* James Gleick, *Patently Absurd*, N.Y. Times Mag., Mar. 12, 2000 (criticizing similar patents).

[13] IBM response to Request for Comments on the International Effort to Harmonize the Substantive Requirements of Patent Law, 66 Fed. Reg. 15,409 (Mar. 19, 2001) *available at* http://www.uspto.gov/web/offices/dcom/olia/harmonization/TAB42.pdf

B. Governments Worldwide Have Struggled to Address the Expanding Scope of Patentability.

The controversy surrounding *State Street* continues to reverberate, fueled by new techniques and strategies to "extract value" from patents. Many of the patents secured by startups during the Internet boom have been bought from their failed owners by companies who are in the business of asserting patents against producers and users of information technology. These "trolls" benefit from the fact that the Federal Circuit has made patents easy to get, easy to assert, more potent, and available without limitation at all levels of granularity and functionality.

The Federal Trade Commission (FTC) and the Department of Justice held a long series of hearings on patents in 2002. The FTC's report, issued in October 2003, demonstrates how differently patents are used and experienced within different sectors of the economy. *See* Federal Trade Commission, *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy* (2003) (hereinafter "FTC Report"). While many problems were common throughout the information technology sector, the "software and Internet" sector (the areas where the subject matter is most abstract) seemed clearly the worst off. The report summarizes the views of the hearing participants:

> Although some panelists stated that software and business method patents foster innovation, many disagreed, asserting that such patents are often questionable and are actually stifling innovation by increasing entry barriers and creating pervasive uncertainty.

FTC Report, ch. 3, at 44.

Testimony from the information technology sector showed how opaque and dysfunctional the system had become, largely as a result of lowered standards and increased incentives to manipulate the system. According to participants, independent invention and inadvertent infringement occurred frequently, reasoned investigation of the patent landscape was burdened by costs and risks, and judicially enhanced incentives invited use of patents not for protection but for extortion. These views contrast dramatically with the sanguine convictions commonly expressed by the patent bar and patent organizations. To be sure, there are winners amidst the chaos, and professional and institutional intermediaries stand to gain from increased levels of activity in all events. It is also true that some of the problems of too many patents are alleviated by practices such as cross-licensing and patent pools, but these responses have effects of their own that are even further removed from the traditional framework of patent jurisprudence.

The Solicitor General's brief opposing certiorari warns of the impact of this case on business expectations: "A decision overturning PTO's approach could call into question a substantial number of patent claims and undermine the settled expectations of numerous participants in technology-based industries." U.S. Br. Opp. Cert. at 14. However, the PTO's approach reflects the jurisprudence of the Federal Circuit, which is directly responsible for the high level of patent-related uncertainty in the information technology sector today. *See* FTC Report, ch. 3, at 14. The FTC repeatedly uses the term "questionable patents" to characterize the problem of uncertainty that pervades the patent system, albeit more so in some sectors than in others. *Id.*

The Solicitor General appears to take into account only the interests of those that own patents, questionable or not. This frames the problem too narrowly since technology producers and users also have an interest in being relieved of unwarranted patent claims. By contrast, the FTC analysis looks at all sides and recommends that policymakers "consider possible harm to competition – along with other possible benefits and costs – before extending the scope of patentable subject matter." FTC Report, Exec. Summ. at 14 (Recommendation 6).

The FTC study is a landmark in that it provides a preliminary understanding of the tradeoffs in patent protection – i.e., how the costs, benefits, risks, and incentives play out under different conditions and circumstances. The case for patents, like the case for antitrust laws, ultimately depends on economic value. The FTC study makes clear that there are major costs in the patent system well beyond the classic costs of monopoly, and that the information technology sector bears more than its share. The burdens include poorly delineated patents, diffuse and ephemeral prior art, an overabundance of information of uncertain value, unavoidable risk of inadvertent infringement, and prohibitive transactions costs. Much of this can be traced to Federal Circuit decisions that have made patents easier to get, easier to assert, more potent, and available without subject matter limitations.

Overseas, the response to the virtually unlimited scope of patentability in the United States has been conspicuously negative. Consultations held by the European Commission and United Kingdom Patent Office in

2000 found that the great majority strongly disfavored business method patents.[14] Given the general parity in commitment to intellectual property protection between the United States and Europe, it is revealing that (in the absence of a judicially created constituency for business method patents) an open political process decisively rejected them. Despite this clear sentiment against business method patents in Europe, the U.S. Government and U.S.-based patent organizations pressed aggressively for patents in all fields of activity, not just technologies. In 2002, the U.S. delegation threatened to walk out of WIPO negotiations for a new substantive patent law treaty (SPLT) if its demand for recognizing business methods was not accepted as "best practice." However, the delegation found no support for this position other than the patent organizations present as observers.[15]

CONCLUSION

The division between free competition and state-sponsored monopoly is one of the great economic problems of our age. The pervasiveness of Internet-enabled enterprise and personal empowerment means that the scope of patentable subject matter affects not only competition between competitors, but the extent to which users of

[14] *See* Consultation Documents of the European Commission (available at http://europa.eu.int/comm/internal_market/en/indprop/comp/softpatanalyse.htm); Consultation Conclusion of the Patent Office of the United Kingdom (available at http://www.patent.gov.uk/about/consultations/conclusions.htm).

[15] World Intell. Prop. Org., *Report of the Seventh Session of the Standing Committee on the Law of Patents* ¶¶ 159-173 (2002), *available at* http://www.wipo.org/scp/en/documents/session_7/pdf/scp7_8.pdf

technology – including individuals, small businesses, and nonprofit organizations – can participate directly in the global agora. This participation is threatened by a U.S. patent system that, driven by self-interested economic and institutional forces, has been transplanted into subject matter beyond its established competence, where a need was never politically expressed and where the system now operates to foment uncertainty and inhibit innovation.

The fruits of this transplantation are bitter, undermining the credibility of our intellectual property laws and breeding contempt for the rule of law in a system dependent largely upon voluntary compliance. To jettison the spurious notion that patent law knows no bounds by enforcing the subject matter limitations of Section 101 of the Patent Act would help repair this damage and restore the credibility of the patent system.

For the reasons set forth above, CCIA respectfully requests that the Court reverse the Federal Circuit.

Respectfully submitted,

BRIAN KAHIN
MATTHEW SCHRUERS
COMPUTER & COMMUNICATIONS INDUSTRY ASSOCIATION
666 Eleventh Street, NW
Washington, DC 20001
(202) 783-0070

JONATHAN BAND
Counsel of Record
JONATHAN BAND PLLC
21 Dupont Circle NW
8th Floor
Washington, DC 20036
(202) 296-5675
jband@policybandwidth.com

Counsel for Amicus Curiae

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IN THE

Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS
(doing business as LabCorp),

Petitioner,

v.

METABOLITE LABORATORIES, INC. and
COMPETITIVE TECHNOLOGIES, INC.,

Respondents.

ON WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

AMICUS CURIAE BRIEF OF THE FEDERAL CIRCUIT BAR ASSOCIATION IN SUPPORT OF RESPONDENTS

PETER B. ELLIS
CLAIRE LAPORTE
FOLEY HOAG LLP
Seaport World Trade
Center West
155 Seaport Boulevard
Boston, MA 02210
(617) 832-1000

MARK P. WALTERS
Counsel of Record
CHRISTENSEN O'CONNOR
JOHNSON KINDNESS PLLC
1420 Fifth Avenue, Suite 2800
Seattle, WA 98101
(206) 682-8100

MARTHA B. SCHNEIDER
PRESIDENT, FEDERAL CIRCUIT
BAR ASSOCIATION
1620 I Street, N.W., Suite 900
Washington, D.C. 20006
(202) 466-3923

Counsel for Amicus Curiae
The Federal Circuit Bar Association

199309

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STATEMENT OF INTEREST OF AMICUS CURIAE

The Federal Circuit Bar Association ("FCBA") is a national organization comprising approximately 2,400 attorneys whose practice concerns the United States Court of Appeals for the Federal Circuit in all aspects of its jurisdiction. The FCBA offers a forum for common concerns and dialogue between the bar and the judges of the Federal Circuit. One purpose of the FCBA is to offer assistance and advice to the Federal Courts, including briefs *amicus curiae*, on matters affecting practice before the Federal Circuit and the law within its exclusive jurisdiction.[1]

Pursuant to Supreme Court Rule 37.2(a), the FCBA has conferred with the parties regarding the filing of this brief *amicus curiae*, and both have consented to its filing. Written evidence of their consent has been filed separately.

Although the FCBA offers this brief in support of the Respondents, it takes no position as to the validity of Claim 13 of U.S. Patent No. 4,940,658 ("the '658 patent"). The FCBA respectfully submits that the Court should dismiss the petition for certiorari as improvidently granted. The only issue even arguably appropriate for certiorari jurisdiction relates to the possible invalidity of Claim 13 for want of patentable subject matter. That issue was not litigated in the lower courts, and this Court should decline to decide the issue on an incomplete record. If, however, the Court chooses to decide the issue of patentable subject matter, the FCBA

1. Pursuant to Supreme Court Rule 37.6, the FCBA represents that no counsel for a party authored this brief in whole or in part. No person or entity, other than the *amicus curiae*, its members, or its counsel, made any monetary contribution to the preparation or submission of the brief.

strongly urges the Court to confine its holdings to the particular facts of this case and in such a way as not to alter existing law. Any broader ruling from this Court on the issue of patentable subject matter could inadvertently disturb the settled and reasonable expectations of those engaged in technology-based industries.

SUMMARY OF ARGUMENT

1. The petition for certiorari should be dismissed as improvidently granted. This Court enjoys discretion to enter such an order, dismissals of this kind often being ordered *sua sponte*. The Court should recognize that the question accepted for certiorari review poses quite discrete issues. Petitioner suggests, initially, that Claim 13 of the '658 patent is invalid as "indefinite, undescribed, and non-enabling": separate issues relating to invalidity under 35 U.S.C. § 112. It then goes on to suggest that Claim 13 also presents an issue of patentable subject matter under § 101. The § 112 issues were litigated in the lower courts; the § 101 issue was not. Petitioner's conflation of these distinct legal issues obscures this important fact. This Court should not depart from its salutary general practice of declining to address issues that were not presented to the courts below.

Moreover, this case does not present a proper record for resolution of the patentable subject matter issue. Claim 13 might well have been construed differently by the lower courts had the issue been raised. Claim construction was litigated vigorously below, with both parties offering widely different interpretations of its scope. The Federal Circuit's eventual opinion evoked a strongly worded dissent on the claim construction issue. The panel majority's claim interpretation is final and unreviewable. This Court enjoys

little or no assurance that any ruling it makes with respect to the § 101 issue will be premised on an accurate claim interpretation.

2. If the Court is inclined to decide the issue of patentable subject matter, the FCBA urges the Court to confine its holdings to the facts of this case and not to alter existing law. For the past quarter-century, reliance on this Court's decision in *Diamond v. Diehr*, 450 U.S. 175 (1981) and the cases therein cited has been widespread and substantial. Consistently with *Diehr* and its predecessors, lower courts have repeatedly ruled that few exceptions exist to the broad categories of patentable subject matter listed in § 101. Extensive Federal Circuit jurisprudence in this area confirms the Congressional judgment that broadly patentable subject matter fosters innovation in technology-based industries such as computer software, pharmaceuticals, and biotechnology, where subject matter is often unpredictable. Nor, during the twenty-five years that have passed since *Diehr*, has Congress seen fit to limit the scope of § 101, even in the wake of decisions confirming the patentability of ever more diverse subject matter. Rather than limiting the potential scope of patents, Congress, when it has seen fit to act, has exempted certain actions or actors from charges of infringement. Statutory exceptions to infringement liability serve as a practical alternative to limiting the categories of subject matter eligible for patent.

Recognizing broadly patentable subject matter does not automatically confer monopoly status. Patent protection remains expressly conditioned upon the other statutory requirements for patentability, including §§ 102, 103 and 112. Restricting the scope of patentable subject matter is not an appropriate means for controlling what some perceive as

improvidently granted patents involving methods of doing business, methods of practicing medicine, diagnostic methods, and the like. In fact, rigorous examination of applications for business method patents has resulted in surprisingly few issued patents relative to the number of filings. This fact confirms that the United States Patent and Trademark Office ("USPTO") is capable of responding adequately to increased filings in an area of newly recognized subject matter.

ARGUMENT

I. The Court Should Dismiss the Petition as Improvidently Granted

A. Historical Background of Certiorari Jurisdiction

The creation of discretionary certiorari jurisdiction over a century ago permitted the Court to control its docket and thus to focus on legal issues of national importance. Justice Frankfurter observed that replacing mandatory jurisdiction with discretionary jurisdiction was necessary if "the proper discharge of the Court's indispensable functions were to be rendered feasible." *Dick v. New York Life Insurance Co.*, 359 U.S. 437, 459 (1959) (Frankfurter, J. dissenting). Discretionary jurisdiction "was not conferred upon this Court merely to give the defeated party in the Circuit Court of Appeals another hearing." *Magnum Co. v. Coty*, 262 U.S. 159, 163 (1923). Today nearly all Supreme Court cases are heard through a discretionary writ of certiorari. Certiorari jurisdiction transformed the Supreme Court "from an error-correcting Court of general appellate jurisdiction to a Court whose special concerns are constitutional interpretation and significant questions of federal law." Chief Justice Rehnquist,

Seen In a Glass Darkly: The Future of the Federal Courts, 1993 WISC. L. REV., Vol. 1, 11 (1993).

The Supreme Court's "indispensable functions" are carried out through careful scrutiny of each petition according to established rules. Supreme Court Rule 10 recites long-held generalizations thought relevant to proper exercise of certiorari jurisdiction. *See Hubbard v. United States*, 514 U.S. 695, 720 (1995) (Rehnquist, C.J. dissenting). Rule 10 warns from the outset that the Court's judicial discretion will be exercised "only for compelling reasons," and adds that "certiorari is rarely granted when the asserted error consists of erroneous factual findings or the misapplication of a properly stated rule of law." The word "important" appears in several places throughout Rule 10, emphasizing that certiorari will not be granted for merely interesting issues. Certiorari jurisdiction is generally confined to importance "beyond the academic or the episodic." *Rice v. Sioux City Cemetery*, 349 U.S. 70, 74 (1955). Even "serious legal questions" may not be sufficiently important for certiorari jurisdiction. *English v. Cunningham*, 361 U.S. 905, 907 (1959). The concept of "importance" relates to the importance of the issues "to the public as distinguished from that of the parties." *Layne & Bowler Corp. v. Western Well Works*, 261 U.S. 387, 393 (1923).

B. The Only Important Issue Presented for Review Relates to Patentable Subject Matter, and This Issue Is Not Reviewable on the Record Below

This Court granted certiorari on the following question:

> Whether a method patent setting forth an indefinite, undescribed, and non-enabling step

> directing a party simply to "correlat[e]" test results can validly claim a monopoly over a basic scientific relationship used in medical treatment such that a doctor necessarily infringes the patent merely by thinking about the relationship after looking at the test result.

(Petition for Certiorari at pp. (i)). Petitioner's question assumes *a priori* that the method at issue includes a step that is "indefinite, undescribed, and non-enabling," three separate and distinct bases for invalidity under § 112. It then suggests that because the claim at issue merely describes "a basic scientific relationship," it cannot be validly patented. This conclusion, if accurate, necessarily implicates § 101. Although introduced through an apparent invocation of § 112, petitioner's question does not suggest any "important" § 112 issue, *i.e.*, one with ramifications extending beyond the facts of this particular case. Indeed, the legal standards codified in § 112 do not invite inquiry into whether a patentee can "validly claim a monopoly over a basic scientific relationship"; rather, they are concerned only with evaluating the adequacy of the patentee's disclosure.

Section 112, ¶ 1 requires a patent applicant to provide a

> written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The second paragraph of § 112 requires the specification to conclude with one or more claims "particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." Section 112 simply does not concern itself with the issue petitioner is actually asking this Court to resolve: whether Claim 13 is inherently unpatentable because it broadly claims the right to exclude others from "thinking" about "a basic scientific relationship." This is an issue that arises, if at all, under § 101. Put another way: even if one accepts that, as Claim 13 was construed by the majority opinion below, "a doctor necessarily infringes the patent merely by thinking about the relationship after looking at the test result," the claim is not therefore "indefinite, undescribed, and non-enabling." On the contrary, logic suggests that only definite, enabled, and described claims could be so easily infringed. In sum, the question as to which certiorari was granted does not raise, either explicitly or implicitly, any "important" issue under § 112.

The petitioner's question does, however, suggest an issue relating to the scope of patentable subject matter under § 101: whether Claim 13 of the '658 Patent is invalid because one cannot patent "laws of nature, natural phenomena, and abstract ideas." *Diehr*, 450 at 185. Indeed, this Court presented the subject matter question to the Solicitor General. *Lab. Corp. v. Metabolite Labs*, 125 S. Ct. 1413, 161 L. Ed. 2d 188 (2005). Declining to offer a definitive answer, the Solicitor General noted that the record on patentable subject matter was not sufficiently developed, and urged the Court to deny certiorari. In support of its position, the Solicitor General cited *Adarand Constructors, Inc. v. Mineta*, 534 U.S. 103, 109 (2001), and *Glover v. United States*, 531 U.S. 198, 205 (2001), two cases stating the general rule that certiorari jurisdiction is normally denied

when the record is unclear and where, as here, the issue for review was also not presented below.

After certiorari was granted in *Adarand*, it became clear that the petitioner was seeking review of a question that had not been directly litigated in the lower court. 534 U.S. at 108. In dismissing the writ, the Court stated "[w]e ordinarily 'do not decide in the first instance issues not decided below.'" (quoting *NCAA v. Smith*, 525 U.S. 459, 470 (1999)). As the Court explained in *Glover v. United States* (citing *Taylor v. Freeland & Kronz*, 503 U.S. 638, 646 (1992)), this rule applies even when certiorari is properly granted on other issues. "In the ordinary course we do not decide questions neither raised nor resolved below." 531 U.S. at 205.

Even assuming that the § 101 subject matter issue is "fairly included" in the petition in compliance with Supreme Court Rule 14.1(a),[2] the Court should decline to decide the

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2. The *Glover* court went on to state that "[a]s a general rule, furthermore, we do not decide issues outside the questions presented by the petition for certiorari." 531 U.S. at 205. (citing Supreme Court Rule 14.1(a)). Supreme Court Rule 14.1(a) states, "[o]nly the questions set out in the petition, or fairly included therein, will be considered by the Court." It is doubtful that the subject matter issue is "fairly included" in the current petition under consideration. Issues of invalidity under § 112 are legally distinct from an issue of patentable subject matter under § 101. Petitioner fails even to cite § 101 as a basis for invalidity in its petition. The petition sets forth arguments traditionally heard during a challenge to patentable subject matter under § 101, but it is unclear that these arguments, framed in terms of § 112, are sufficient to comply with Rule 14. This Court's decisions suggest that strict compliance with Rule 14 is required, refusing on more than one occasion to address issues not "fairly included" in a petition. *See, e.g., Thornton v. United States*, 541 U.S.

(Cont'd)

issue. The proper scope of Claim 13 was hotly disputed by the parties below; indeed, as the dissent below illustrates, even the panel that decided the case could not reach agreement on the proper construction of that claim. *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1372 (Fed. Cir. 2004) (Schall, J., dissenting). Patentability under § 101 depends directly upon a proper claim construction. *State Street Bank & Trust Co. v. Signature Financial Group*, 149 F.3d 1368, 1370 (Fed. Cir. 1998) ("Whether the . . . patent is invalid for failure to claim statutory subject matter under § 101, is a matter of both claim construction and statutory construction."). Here, the claim construction adopted by the trial and appellate courts might well have been different had the § 101 issue been raised. For example, the "assay" limitation of Claim 13 could have been construed in such a manner as to avoid the issue that petitioner now asserts. *See, e.g., Liebel Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 911 (Fed. Cir. 2004) (reciting general rule that "claims should be so construed, if possible, as to sustain their validity.").

Here, the lower court did not interpret the "assay" limitation of Claim 13. Had it considered a challenge to the subject matter of Claim 13, the "assay" limitation could have been limited to a step involving "[t]ransformation and reduction of an article 'to a different state or thing.'" *Gottschalk v. Benson*, 409 U.S. 63, 70 (1972). Transformation or reduction of an article to a "different state or thing" has long served as a key sign that a method claim is drawn to

(Cont'd)

615, 624 (2004); *Jones v. United States*, 527 U.S. 373, 394 n.11 (1999); *Phillips v. Wash. Legal Found.*, 524 U.S. 156, 184 n.4 (1998) (reasoning that "it would be improper for us *sua sponte* to raise and address the question. . . .").

patentable subject matter. *Diehr*, 450 U.S. 184 (quoting *Benson*, 409 U.S. at 70; *see also Parker v. Flook*, 437 U.S. 584, 588-589 & n.9 (1978); *Cochrane v. Deener*, 94 U.S. 780, 787-788 (1876)). The Solicitor General rightly notes that the term "assay" is generally understood to refer to "[t]he quantitative analysis of a substance to determine the proportion of some valuable or potent constituent ." (Br. of the Sol. Gen. at p. 9, citing LAROUSSE DICTIONARY OF SCIENCE AND TECHNOLOGY 64 (Peter M.B. Walker ed., 1995)). This definition implies a transformation of matter, however, the factual record in this case is not adequately developed on this point. It is at least possible that other methods of measuring total homocysteine levels would not involve a transformation of matter.

The importance of claim construction to proper resolution of the patentable subject matter issue cannot be overemphasized — but claim construction is not before this Court. The Court has explained that prior to engaging in a § 101 subject matter inquiry, the Court should determine "what type of discovery is sought to be patented." *Flook*, 437 U.S. at 593. "In determining the eligibility of respondents' claimed process for patent protection under § 101, their claims must be considered as a whole." *Diehr*, 450 U.S. at 188; *Flook*, 437 U.S. at 594 & n.16. Here, the limitations of Claim 13 were never considered by the courts below or by the parties in the context of a subject matter challenge. As previously noted, claim construction presented a close issue, as to which one of the three panel members dissented. *See Metabolite Labs.*, 370 F.3d at 1372 (Schall, J., dissenting). Petitioner's failure to raise the patentable subject matter issue below deprived the courts and Respondents of an opportunity to address claim construction in light of § 101. It also means that this Court is, in effect,

"stuck" with a claim construction ruling that could be inaccurate or that was, at the very least, not fully considered in light of an adequately developed factual record. In this context, the Court should decline to address the § 101 issue.

In numerous similar cases, this Court has dismissed the petition as improvidently granted. *Wainwright v. City of New Orleans*, 392 U.S. 598, 599 (1968) (dismissing petition because record was "too opaque" and "too sketchy"); *see also, Kimbrough v. United States*, 364 U.S. 661 (1961) (dismissing petition because the question was not "presented with sufficient clarity in this case"); *Mitchell v. Oregon Frozen Foods Co.*, 361 U.S. 231 (1960) (dismissing petition because "ambiguities in the record as to the issues sought to be tendered" appeared); *Rogers v. United States*, 522 U.S. 252, 258-59 (1998) (same); *McCarthy v. Bruner*, 323 U.S. 673 (1944) (same). In one such case, Justice Frankfurter explained:

> [c]onsidering the volume of cases which invoke the Court's discretionary jurisdiction — as of today 1,091 such cases have been passed on during this Term[3] — it would be indeed surprising if in each Term there were not two or three instances of petitions which, after passing through the preliminary sifting process, did not survive the scrutiny of oral argument.

Needelman v. United States, 362 U.S. 600, 601 (1960). The Court should make a similar determination here.

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3. According to the Supreme Court's Public Information Office, more than eight times as many cases were considered during the October Term 2004 (8,588), and the Court has already considered over five times as many this Term (5,654 and counting).

II. Any Decision of the Court on the Issue of Patentable Subject Matter Should be Confined to the Facts of This Case and Should Not Alter Existing Law

If, notwithstanding the considerations discussed above, the Court elects to decide the belatedly raised issue of patentable subject matter, the FCBA respectfully urges the Court to confine both its holding and any dicta to the facts of this case, and to ensure that its ruling does not extend beyond prior precedent in this area. Any broader ruling by this Court on the scope of patentable subject matter could inadvertently disturb well-settled and entirely reasonable expectations held by those engaged in technology-based industries.

A. Historical Development of Federal Circuit Subject Matter Jurisprudence

Shortly after this Court's decision in *Diehr*, the United States embarked on a "juridical experiment" by establishing the Federal Circuit Court of Appeals, "the only major change in federal court structure in a hundred years." Judge Pauline Newman, Foreword: *The Federal Circuit in Perspective*, 54 AM. U. L. REV. 821 (2005). At a time when it was widely believed that a "diminished capability of patents to support investment in new or improved products contributed to the weakness of the economy," creation of the Federal Circuit was intended to "reinvigorate the nation's industrial strength and technological leadership, with the assistance of a revived and effective patent system." *Id.* at 822. "It was recognized then, as now, that our economic strength as a nation depends on technologic leadership, the balance of trade, and a culture that favors creativity, entrepreneurship, and industrial activity. These aspects can be fostered or deterred by governmental policy." *Id.* at 821.

This Court's decision in *Diehr* and its predecessors laid the legal foundation upon which the Federal Circuit has consistently reinforced the view that there are very few exceptions to the broad categories of patentable subject matter listed in § 101. "We have come a long way from the days when judges frowned on patents as pernicious monopolies deserving scant regard. Today, patents are the backbone of much of the national economy, and, as this court has recently held, virtually anything is patentable." *Hughes Aircraft Co. v. United States*, 148 F.3d 1384, 1385 (Fed. Cir. 1998) (citing *State Street*, 149 F.3d at 1368). The last twenty-five years have seen rapid innovation in newly-emerging fields, especially in computer software and biotechnology. The U.S. patent system has repeatedly adapted to and in most cases, embraced new technologies.

In 1994, the Federal Circuit decided *In re Alappat*, 33 F.3d 1526 (Fed. Cir. 1994), a case widely credited with encouraging the USPTO's current approach to software patent applications. Elaborating on the principles set out in *Diehr*, the Federal Circuit commented that:

> the proper inquiry in dealing with the so called mathematical subject matter exception to § 101 alleged herein is to see whether the claimed subject matter as a whole is a disembodied mathematical concept, whether categorized as a mathematical formula, mathematical equation, mathematical algorithm, or the like, which in essence represents nothing more than a "law of nature," "natural phenomenon," or "abstract idea." If so, *Diehr* precludes the patenting of that subject matter. That is not the case here.

Id. at 1544. *Alappat* set the stage for a wealth of innovation over the next decade in the fields of software and Internet communications.[4] Four years after *Alappat*, the Federal Circuit decided *State Street*, 149 F.3d at 1370, eliminating pre-existing confusion over the patentability of business methods. Since *State Street*, the USPTO has issued hundreds of patents on inventions drawn to methods of doing business.[5]

B. There is No Compelling Reason to Change the Current Law on Patentable Subject Matter

Any decision from this Court disturbing its own prior precedent or the view of § 101 currently held by the Federal Circuit and the USPTO would call into question a substantial number of patent claims and disrupt reliance on the patent system by numerous technology-based companies. As noted by the Solicitor General,

> The number of patent claims that would be invalidated by a reversal of the Federal Circuit's understanding of *Flook* and *Diehr* is difficult to predict, and would depend in part on the rule of law adopted by this Court. At a minimum,

4. According to some estimates, computer software and Internet patents represent more than fifteen percent of all patents currently issued by the USPTO. *See* Allen Clark Zoracki, Comment: *When is an Algorithm Invented? The Need for a New Paradigm for Evaluating an Algorithm for Intellectual Property Protection.* 15 ALB. L. J. SCI. & TECH. 579, 585 n. 26 (2005).

5. Statistics from the USPTO indicate that only a very small fraction (less than 5%) of all applications claiming methods of doing business are allowed to issue. *See infra*, note 6 and accompanying text.

> however, a paradigm shift in the way PTO and the lower courts have viewed *Diehr* would engender substantial uncertainty.

(Br. of the Sol. Gen. at p. 15.)

For the past quarter-century, the Federal Circuit has taken the view, consistent with *Diehr* and predecessor cases, that there are few exceptions to § 101. One reason for this policy is that judicially created exceptions to patentable subject matter have often proven hard to administer in practice. Before the Federal Circuit's decision in *State Street*, "patent applicants often resorted to contorted claim drafting techniques in order to avoid the exclusionary rules of patent eligibility." John R. Thomas, *Formalism at the Federal Circuit*, 52 AM. U. L. REV. 771, 789 (2003). As Judge Rader remarked, pre-*State Street* law, which invoked numerous judge-made exceptions to § 101 in the field of computer software and business methods, was a "twisted knot of precedent." *Arrhythmia Research Tech. Inc. v. Corazonix Corp.*, 958 F.2d 1053, 1061 (Fed. Cir. 1992) (Rader, J. concurring). Some commentators have likened pre-*State Street* law to the "Byzantine strands forming a Gordian knot, finding them easier to sever than to untie." Thomas, *supra*, at 789 (citations omitted). History shows that judicial exceptions to § 101 tend to create more problems than they solve. If Congress deemed it necessary, it could amend § 101, but it has left the scope of § 101 unaltered notwithstanding a debate that is far older than the statute itself.

C. Congress Has Left § 101 And Its Broad Categories Of Eligible Subject Matter Alone

The language of § 101 has remained unchanged since 1952, even in the face of decisions such as *State Street* that have confirmed the patentability of increasingly more diverse subject matter. Instead of amending § 101 to restrict the classes of eligible subject matter, Congress has passed exceptions to infringement. For example, Congress has amended 35 U.S.C. § 287, which now reads in relevant part:

> (c)(1) With respect to medical practitioner's performance of a medical activity that constitutes an infringement under section 271(a) or (b) of this title, the provisions of sections 281, 283, 284, and 285 of this title shall not apply against the medical practitioner or against a related health care entity with respect to such medical activity.

Congress passed this provision specifically to address newly patented methods of practicing medicine, out of concern that patents on methods of practicing medicine could negatively affect public health. *See* H.R. Rep. No. 104-863, pt. 7, at § 616 (1996); *see also* Gerald J. Mossinghoff, Article, *Remedies Under Patents on Medical and Surgical Procedures*, 78 J. PATENT & TRADEMARK OFFICE SOC. 789 n. 17 (1996). Patents on novel methods of practicing medicine may prevent some doctors and hospitals from providing the best medical care known to the profession, so Congress thought it appropriate to provide medical care providers with limited protection from infringement liability. *Id.* (discussing lawsuit filed by Samuel L. Pallin against Dr. Jack A. Singer alleging infringement of U.S. Patent No. 5,080,111.) Congress specifically excluded other business entities such as

Petitioner from the protection of § 287(c)(1) by providing that the exception does not apply to "clinical laboratories services" like those at issue in this case. *See* § 287(c)(3). Congressional protection of certain actors or actions from charges of infringement is a preferable alternative to judge-created exceptions to the broad "method" category listed in § 101.

D. Broadly Patentable Subject Matter Must Still Be Novel and Non-Obvious Before a Patent Is Granted

Debate over the appropriate scope of protectable subject matter rages on, especially in the wake of the Federal Circuit's decision in *State Street*. Some see broadly patentable subject matter under § 101 as harmful to the economy because it includes methods of doing business. *See* Jay Dratler, Jr., Article: *Alice in Wonderland Meets the U.S. Patent System*, 38 AKRON L. REV. 299, 308-310 (2005). Others argue that patent incentives for inventions covering software and business methods do little to promote innovation. *See, e.g.*, Robert M. Hunt, Article: *You Can Patent That? Are Patents on Computer Programs and Business Methods Good for the Economy?*, BUSINESS REVIEW Q1 at p. 8 (Federal Reserve Bank of Philadelphia 2001) available at http://www.phil.frb.org/files/br/brq101bh.pdf (last visited on December 21, 2005). "Firms in the computer software and financial services industries were innovating rapidly long before it was thought possible to patent their innovations, yet they found effective ways to exploit their innovations without patents." *Id.* The Federal Trade Commission has also weighed in on the debate:

> The constitutional intention that patents 'promote the progress of science and useful arts' should be

> taken into account in interpreting the scope of patentable subject matter under § 101. Decision makers should ask whether granting patents on certain subject matter in fact will promote such progress or instead will hinder competition that can effectively spur innovation.

To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy, a Report by the Federal Trade Commission (October 2003), available at http://www.ftc.gov/reports/index.htm (containing an index to the document in Acrobat format) (last visited December 21, 2005).

While an improvidently granted patent creates potential for economic harm, that harm is substantially outweighed by the harm that would be inflicted through judicial policy that broadly and unnecessarily restricts the scope of patentable subject matter. The risk of inappropriate patent protection is best controlled by rigorous application, on a case-by-case basis, of the other statutory requirements for patentability, §§ 102, 103, and 112. In fact, the USPTO has shown itself capable of responding to the concerns expressed by some regarding the statutory breadth of potentially protectable subject matter. Since *State Street*, the USPTO has seen a flood of applications in Class 705, which pertains to business method patent applications. *See USPTO White Paper on Automated Financial or Management Data Processing Methods (Business Methods)* (2001) available at http://www.uspto.gov/web/menu/busmethp /index.html (last visited on December 21, 2005). In response to the increased volume of such applications, the USPTO has changed its examination procedures in Class 705, requiring more robust searches for prior art, second reviews of applications, and more patent examiners. *See id.* Rigorous examination in

Class 705 has resulted in surprisingly few patents being issued in comparison to the number of filings. In 2004, just 282 patents were issued in Class 705, while some 6,200 applications were filed. *See Class 705 Application Filing and Patents Issue Data* (October 31, 2004) available at http://www.uspto.gov/web/menu/pbmethod/ applicationfiling.htm (last visited December 21, 2005).[6] In light of these statistics, the alarm sounded by some in the wake of *State Street* seems unjustified. *See, e.g.*, Dratler, *supra*, at 308-310.

Rigorous examination focused on §§ 102, 103, and 112 is the most practical and economically sensible way to prevent the issuance of inappropriate patents. By contrast, broadly restricting patentable subject matter in an effort to eliminate improvidently granted patents could well do greater economic harm. Any further judicially created restrictions on the scope of § 101 would inevitably create uncertainty and would likely result in numerous challenges to existing patents, thereby disturbing many economic actors' reasonable reliance on what was previously thought to be well-settled law. Indeed, such restrictions might well impair incentives for innovation in inherently risky technology-based industries.

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6. There is typically a delay of thirty-six months to the first Office Action on the merits of applications filed in Class 705, and a forty-two-month average disposal time with an application moving to issue or abandonment. In 2000, there were 7,800 applications filed in Class 705 and in 2001 there were 8,700 applications filed in Class 705. *See Application Filing Data, supra.*

CONCLUSION

For the reasons set forth above, the petition should be dismissed as improvidently granted. In the alternative, if the Court decides to address the § 101 issue, the FCBA respectfully urges the Court not to depart from or expand upon its own long-established precedent and to confine its ruling to the facts of this case.

Respectfully submitted,

PETER B. ELLIS
CLAIRE LAPORTE
FOLEY HOAG LLP
Seaport World Trade
Center West
155 Seaport Boulevard
Boston, MA 02210
(617) 832-1000

MARK P. WALTERS
Counsel of Record
CHRISTENSEN O'CONNOR
JOHNSON KINDNESS PLLC
1420 Fifth Avenue, Suite 2800
Seattle, WA 98101
(206) 682-8100

MARTHA B. SCHNEIDER
PRESIDENT, FEDERAL CIRCUIT
BAR ASSOCIATION
1620 I Street, N.W., Suite 900
Washington, D.C. 20006
(202) 466-3923

Counsel for Amicus Curiae
The Federal Circuit Bar Association

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No. 04-607

In the Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS (D/B/A LABCORP),

Petitioner,

v.

METABOLITE LABORATORIES, INC., AND COMPETITIVE TECHNOLOGIES, INC.,

Respondents.

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On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF FINANCIAL SERVICES INDUSTRY *AMICI CURIAE* IN SUPPORT OF REVERSAL

DONALD M. FALK
Counsel of Record
Mayer, Brown, Rowe & Maw LLP
Two Palo Alto Square, Ste. 300
3000 El Camino Real
Palo Alto, CA 94306
(650) 331-2000

JEREMY GASTON
Mayer, Brown, Rowe & Maw LLP
700 Louisiana, Ste. 3600
Houston, TX 77002
(713) 221-1651

Counsel for Amici Curiae

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STATEMENT OF INTEREST OF *AMICI CURIAE*

Bear, Stearns & Co. Inc. and Lehman Brothers Inc. (collectively "Financial Services *Amici*") are among the leading participants in the financial services industry. The Financial Services *Amici* are participating in this case out of a deep concern about the threat to innovation—and thus to consumer welfare—posed by patents that claim exclusive rights to abstract ideas.[1]

As the facts of this case demonstrate, abstract ideas, whether in the form of known observations about natural phenomena or otherwise, now may be patented under current Federal Circuit precedent and, consequently, Patent and Trademark Office ("PTO") practice. The breadth and abstraction of the correlation step in the patent under review finds parallels in the many abstract ideas or insights about doing business that have received patent protection.

The Court's decision on the issues in this case relating to the proper scope of patentable subject matter could have significant economic repercussions. In particular, if in deciding this case the Court were to countenance patents that claim abstract ideas, the free-for-all in the patenting of abstract business methods would continue and undoubtedly hinder innovation and efficiency in the financial services industry for decades. In the last several years, business method patents already have purported to claim monopoly control over investment strategies. Yet, before the Federal Circuit's decision in *State Street Bank & Trust Co.* v. *Signature Financial Corp.*, 149 F.3d 1368, 1373 (1998), financial instruments and

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[1] Pursuant to Rule 37.3, the parties have consented to the filing of this brief and their consent letters have been lodged with the Clerk of the Court. Pursuant to Rule 37.6, the Financial Services *Amici* state that no counsel for a party has written this brief in whole or in part and that no party or entity, other than the Financial Services *Amici*, their members or their counsel has made a monetary contribution to the preparation or submission of this brief.

investment practices evolved and flourished within a competitive atmosphere that has made America's financial services industry the undisputed world leader without the need for government-granted monopolies over methods of doing business. Consumers reap the benefits of this strong and unimpeded competition, and should not be deprived of those benefits through an unwise extension of the scope of patentable subject matter beyond the boundaries contemplated by the terms of the Patent Code and by the constitutional provision authorizing the issuance of patents.

In approving and encouraging broad claims whose only point of novelty is a natural phenomenon or abstract idea, the Federal Circuit has departed from limits on patentable subject matter that this Court has consistently recognized in its decisions, most recently in *Diamond* v. *Diehr*, 450 U.S. 175 (1981). In addition, as this case illustrates, patents that assert claims to natural phenomena or abstract ideas almost necessarily raise issues of indefiniteness and inadequate description as well, impeding the notice function of the patent system to the detriment of innovation and consumer welfare.

This Court can and should reduce the risk to innovation and efficiency in the financial services industry by reaffirming that the patentability principles enunciated in *Diehr* and earlier cases. Those principles, by requiring that a patentable process produce an alteration in matter, exclude from the scope of patentable subject matter the mere invocation of abstract ideas, including known relationships among natural (or marketplace) phenomena. The Court has been equally clear that an abstraction does not become patentable merely by adding a token activity—"implementing" an idea in a business, or processing a formula on a computer. Abstractions may be ***included*** in a patentable claim if they are part of a novel process that produces a tangible result in the physical world, but mere insights or commercial principles should not be patentable in themselves.

ARGUMENT

The central issue in this case is whether a patent may monopolize the mental process of arriving at a conclusion based on pre-existing medical and chemical knowledge. That question has great import in the financial services industry because patents on abstract business methods similarly purport to claim general commercial principles and their application through thought or interpersonal management, without any tangible alteration to the physical world.

I. The Indefiniteness And Inadequate Description In This Case Are Symptoms Of An Artful Attempt To Claim Unpatentable Subject Matter.

The patent claim before this Court claims a "method" consisting of two steps: (1) "assaying a body fluid for an elevated level of total homocysteine"; and (2) "correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalmin or folate." Pet. App. 3a. As the petitioner has explained, these two claimed steps are indefinite and inadequately described because they merely identify general types of effort without explaining exactly what a person must do to perform the assay or correlation, in effect relying on additional *un*claimed steps.

The claim at issue appears to have been carefully drafted to capture a patent monopoly over physicians' pre-existing knowledge of chemical reactions involving homocysteine, folate, and cobalmin in the body, that is, known natural laws and phenomena. See Ruma V. Banerjee and Rowena G. Matthews, *Cobalamin-Dependent Methionine Synthase*, 4 FASEB JOURNAL 1450, 1450 (1990). Yet the patent could not claim that knowledge explicitly: a patent "claim covers and secures a process, a machine, a manufacture, a composition of matter, or a design, but never the function or result of either, nor the scientific explanation of their operation." *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 373 (1996).

The Federal Circuit nonetheless openly acknowledged that the "centerpiece of the invention" at issue here was the vaguely described mental process of assessing natural phenomena. Pet. App. 18a. By approving the use of the indefinite word "correlate," the Federal Circuit expanded the patent monopoly to include unpatentable abstract ideas. As this Court warned in *Markman*, however, indefinite language must not be used to expand the patent monopoly because "[t]he limits of a patent must be known for the protection of the patentee, the encouragement of the inventive genius of others and the assurance that the subject of the patent will be dedicated ultimately to the public." 517 U.S. at 390.

Although this Court has not explicitly addressed the interaction between indefiniteness and the limits on patentable subject matter, it has rejected efforts to circumvent those limits through artful drafting that merely places an abstract idea in a particular technical context:

> A mathematical formula as such is not accorded the protection of our patent laws, and this principle cannot be circumvented by attempting to limit the use of the formula to a particular technological environment. Similarly, insignificant post-solution activity will not transform an unpatentable principle into a patentable process. To hold otherwise would allow a competent draftsman to evade the recognized limitations on the type of subject matter eligible for patent protection.

Diamond v. *Diehr*, 450 U.S. 175, 191-92 (1981). The correlation step in the patent at issue in this case reflects exactly the kind of window-dressing atop an abstract idea that this Court strongly disapproved in *Diehr*. And it recalls many patents on abstract business methods that assert claims to insights about market, customer, or employee behavior.

In explicating the limits on patentable subject matter, and in disapproving the use of drafting to avoid them, this Court has preserved the "delicate balance" between the rights of the

public and inventors. *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 730-31 (2002). That balance requires clarity both as to what ***is*** claimed in a particular patent (*ibid.*) and to what ***may*** be claimed in the first place. By upholding the abstract patent claim here, the Federal Circuit allowed artful drafting to upset that balance.

II. This Court Should Address And Resolve The Underlying Problem Posed By The Federal Circuit's Refusal To Maintain Strict Limits On The Use Of Patents To Claim Monopolies Over Abstract Ideas.

Although it is not apparent from the result below, the law imposes limits on the types of activities and endeavors that may be patented. The Patent Code permits a patent to issue only on a "new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." 35 U.S.C. § 101. This Court has held that certain subject matter does not fall within the recited scope. In particular, the Court has concluded that "laws of nature, natural phenomena, and abstract ideas" cannot be patented. *Diehr*, 450 U.S. at 185; see also *Diamond* v. *Chakrabarty*, 447 U.S. 303, 309 (1980) (referring to "physical phenomena"). Grouping laws of nature and natural phenomena together with abstract ideas is logical because, as expressed in a patent, a law of nature (like the chemical relationship at issue here) that has been reduced to human understanding is a type of abstract idea: namely, an abstraction from the physical world that identifies a pre-existing relationship or operation of matter in nature. See, *e.g.*, *Funk Brothers Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 131 (1948) (rejecting patent that purported to claim operation of certain bacteria on plants).

As a consequence, the relation between indefiniteness, inadequate description, and unpatentable subject matter outlined above is not limited to patents involving natural laws, but extends to all patents involving abstract ideas in the commercial as well as in the scientific context. Artful at-

tempts to patent abstract ideas may result in indefinite claims and inadequate descriptions, as shown above, but those are only symptoms of a more fundamental problem: the acquiescence of the Federal Circuit and the PTO in the patenting of abstract ideas. This problem is growing because the Federal Circuit has strayed from this Court's limits on patentable subject matter.

This Court has expressed those limits clearly enough when explaining what processes are patentable. In *Diehr*, the Court limited patent protection to processes that transform or reduce a physical article to another physical state or thing. 405 U.S. at 192. The Court drew on its precedents holding that a patentable "process requires that certain things should be done with certain ***substances***." *Id.* at 183-84 (quoting *Cochrane* v. *Deener*, 94 U.S. 780, 788 (1877)).

The Court also has addressed and rejected efforts to make an abstract idea patentable by such expedients as "limiting the use of [a] formula to a particular technological environment" or to "a particular technological use," *Diehr*, 450 U.S. at 191, 192 n.14, or by reciting some trivial and non-novel physical activity to take place after an abstract idea has been expressed. In the context of a patent that claimed the process of solving a mathematical formula, the Court pointedly held that "insignificant post-solution activity will not transform an unpatentable principle into a patentable process." *Id.* at 191-92. In so holding, the Court balanced the public's interest in free access to already-present "laws of nature, natural phenomena, and abstract ideas," against Congress' intent to extend patent protection to "anything under the sun that is made by man." Compare *id.* at 185, with *id.* at 182.

The Federal Circuit formerly paid lip-service to *Diehr*, holding that processes involving abstract ideas could not be patented unless their application produced a "useful, concrete, and tangible result." *In re Alappat*, 33 F.3d 1526, 1544 (Fed. Cir. 1994) (en banc). In more recent decisions, how-

ever—including the one under review—the Federal Circuit has dropped the requirements of concreteness and tangibility. Instead, that court allows trivial activity to render an abstract price calculation patentable. Thus, in its seminal *State Street* decision, the court forthrightly held that the mere "transformation of data, representing discrete dollar amounts, by a machine through a series of mathematical algorithim, formula, or calculation into a final share price" could receive a patent. 149 F.3d at 1373. The "tangible result" was "a final share price momentarily fixed for recording and reporting purposes." *Ibid.* That is, an abstract idea became patentable once it was expressed in a computer memory.

Although the patent in *State Street* claimed a machine that performed the recited process (through a means-plus-function claim, see 35 U.S.C. § 112 ¶ 6), the process, not the generically claimed "means," provided the point of novelty. The mere expedient of claiming the (unexceptional) computer that processes an abstract formula does not render the patent less abstract, or more compliant with 35 U.S.C. § 101. As Justice Story observed long ago, if a machine is "old and well known, and applied only to a new purpose, that does not make it patentable." *LeRoy* v. *Tatham*, 14 How. (55 U.S.) 156, 177 (1853) (quoting *Bean* v. *Smallwood*, 2 Story Rep. 408, 2 F. Cas 1142, 1143 (C.C.D. Mass. 1843) (Story, J.)).

Computers provide particularly ill-suited means to transform an unpatentable idea into a patentable process. To begin with, the functions that computers perform are qualitatively no different than mental processes. If those processes are not patentable when conducted in the mind or with paper and pencil, then they should not be patentable when conducted through software. As this Court recognized, if the use of an algorithm on a computer could be patentable, then that "in practical effect would be a patent on the algorithm itself." *Gottschalk* v. *Benson*, 409 U.S. 63, 72 (1972). Moreover, a computer exception would swallow the rule, as almost all abstract ideas—especially mathematical algorithms and for-

mulas implicated in abstract business method patents—may be implemented as software on a computer. Finally, although computer implementation may involve physical objects such as electrons, the transformations of matter that occur are not material to an invention that relies on the abstract content of a program or formula, as this Court implicitly recognized in *Benson* and *Parker* v. *Flook*, 437 U.S. 584, 590 (1978). "The end product" of a computer run is not anything so tangible as the "precisely cured rubber as it was in *Diehr* but rather different data as a mathematical function of the original data." *In re Alappat*, 33 F.3d 1526, 1564-1565 (Fed. Cir. 1994) (en banc) (Archer, J., dissenting).

Perhaps the most fundamentally troubling aspect of the *State Street* analysis is this: Any application of a mathematical algorithm that produces a price or other value used in a market transaction might be a patentable process under § 101 (though, of course, it would have to satisfy the novelty and other criteria for patentability as well). But that analysis conflicts with *Diehr*. The patented process does not "transform[] or reduc[e] an article to a different state or thing." *Diehr*, 450 U.S. at 192. Moreover, the use of a mathematical formula's output to set a price—like the processing of a formula on a computer—is exactly the type of "token post-solution activity" (*id.* at 192 n.14) that cannot "transform an unpatentable principle into a patentable process" (*id.* at 191-92).

The Federal Circuit extended its endorsement of the patenting of abstract ideas when it approved a patent on the use of simple Boolean algebra—a universally known mathematical algorithm—to generate numbers useful in identifying a telephone customer's long-distance carrier. The court of appeals held that this claimed use of a formula raised no meaningful questions of patentability "[b]ecause the claimed process applies the Boolean principle" for a particular technical purpose "without pre-empting other uses of the mathe-

matical principle." *AT&T Corp.* v. *Excel Communications, Inc.*, 172 F.3d 1352, 1358 (Fed. Cir. 1999).

That holding conflicts with this Court's conclusion that "[a] mathematical formula does not suddenly become patentable subject matter simply by having the applicant acquiesce to limiting the reach of the patent for the formula to a particular technological use." *Diehr*, 450 U.S. at 192 n.14. Yet the Federal Circuit characterized this Court's repeated pronouncements in *Diehr* linking patentable processes with physical effects as providing mere examples rather than a limiting principle. 172 F.3d at 1358-59. But see *Diehr*, 450 U.S. at 182 n.7 (quoting *Corning* v. *Burden*, 56 U.S. (15 How.) 252, 268 (1853), to the effect that patentable processes involve a "result or effect [that] is produced by chemical action, by the operation or application of some element or power of nature, or of one substance to another"); *Diehr*, 450 U.S. at 183 (quoting *Cochrane*, 94 U.S. at 788 (patentable process is a "mode of ***treatment of certain materials*** to produce a given result" (emphasis added)).

In two short steps, the Federal Circuit effectively nullified this Court's reservation of abstract ideas to the public domain—and attracted significant academic criticism in the process.[2] Now claims that would be utterly unpatentable under a common-sense reading of *Diehr* fall "comfortably * * * within the scope of [35 U.S.C.] § 101" as interpreted by the Federal Circuit. *Excel Communications*, 172 F.3d at 1358. As this Court warned long ago, without principled policing of the boundaries of patentable subject-matter, "every shadow

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[2] See, *e.g.*, Robert P. Merges, *As Many as Six Impossible Patents Before Breakfast: Property Rights for Business Concepts and Patent System Reform*, 14 BERKELEY TECH. L.J. 577 (1999); Leo J. Raskind, *The State Street Decision: The Bad Business of Unlimited Patent Protection for Methods of Doing Business*, 10 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 61, 61 (1999) (describing *State Street* as a "sweeping * * * departure from precedent").

of a shade of an idea" may be patentable. *Atlantic Works* v. *Brady*, 107 U.S. 192, 200 (1881). That is precisely the course that the Federal Circuit has chosen with its nearly standardless approach, at high cost to the financial service industry's competitive environment.

III. The Federal Circuit's Expansion Of Patentable Subject Matter Has Encouraged The PTO To Issue Patents On Abstract Business Methods.

Under the Federal Circuit's recent decisions, patentees now may seize monopolies on particular ways of doing business by claiming protection for the abstract ideas that underlie the creation of an investment product or a management scheme. Unsurprisingly, annual applications for patents on business methods have risen from the low hundreds in 1995 to more than 6000 today.[3]

The explosion in business method patent applications is easy to explain: The Federal Circuit's departure from this Court's guidance made virtually any use of a natural phenomenon, mathematical algorithm, or other abstract idea potentially patentable. Business processes fit this bill; the use of computers and, in many cases, the Internet to do business provided a fig-leaf sufficient to make old practices seem new and superficially technological. Moreover, many remunerative business activities—especially in the financial services industry—consist of processing mathematical algorithms on computers in conjunction with Internet-based communication. As a consequence, applications have poured in.

In response to the Federal Circuit's decisions, the PTO has instructed its patent examiners to take an extremely broad view of patentability. An example provided in a 2001 PTO examiner training course emphasized how insignificant post-

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[3] See U.S. Patent and Trademark Office, Class 705 Application Filing and Patents Issued Data, *available at* http://www.uspto.gov/web/menu/pbmethod/applicationfiling.htm.

solution activity could be and still satisfy *State Street* and *Excel Communications*. The trainers imagined the following patent claim:

> Claim 1. A method comprising the steps of:
>
> (a) convening people in a room; and
>
> (b) brainstorming to generate a series of steps forming a scheme for reducing the number of patent applications pending in the Technology Center.

U.S. PTO, 35 U.S.C. § 101 Training Materials, Slide 23 (ca. Aug. 5, 2001), *available at* http://web.archive.org/web/20010805115843 (search term: http://www.uspto.gov/web/menu/pbmethod/trangmaterials.ppt). This claim was unpatentable beause it "merely manipulated an abstract idea without producing a useful, concrete and tangible result." *Id.* at Slide 24. But according to the PTO Trainers, adding the following dependent claim allowed the earlier claim to meet the Federal Circuit's test:

> The method of Claim 1, further comprising the step of * * * ***implementing the steps of the scheme***.

Id. at Slide 26 (emphasis added). This is exactly the sort of insignificant (and indefinite) addition to a claim for an abstract idea that this Court held insufficient in *Diehr*, 450 U.S. at 191-92.

The Board of Patent Appeals and Interferences confirmed this exceptionally broad view of patentability in a recent precedential decision, *Ex parte Lundgren*, Appeal No. 2033-2088, Application 08/093,516, 2004 WL 3561262 (heard Apr. 20, 2004). Lundgren claimed a method for setting compensation for managers using competitive benchmarks.[4] That method consisted merely of applying a mathematical algo-

[4] Lundgren already owns a patent for a "Method of eliciting unbiased forecasts by relating a forecaster's pay to the forecaster's contribution to a collective forecast." Patent No. 5,608,620.

rithm designed to prevent collusion among managers in a given comparison group and adding this token step:

> transferring compensation to said manager, said transferred compensation having a value related to said managerial compensation amount [determined by applying the mathematical algorithm].

2004 WL 3561262, at *1.

The examiner rejected the application as an unpatentable effort to claim "an economic theory expressed as a mathematical algorithm" (*id.* at *2), but the Board reversed, chiding the examiner in these terms:

> Since the Federal Circuit has held that a process claim that applies a mathematical algorithm to "produce a useful, concrete, tangible result without pre-empting other uses of the mathematical principle, on its face comfortably falls within the scope of § 101," one would think there would be no more issues to be resolved under [35 U.S.C.] § 101.

Id. at *3 (quoting *Excel Communications*, 172 F.3d at 1358).

In particular, the Board rejected that notion a patent needed to involve any "technological arts" that would distinguish the claims from an effort to patent mental processes. *Id.* at *3. The Board did not acknowledge this Court's concrete, tangible formulation of the scope of patentable processes in *Diehr*. Rather, the Board concluded, because this Court made "no reference * * * to the [PTO's then-]new technological-arts standard" in *Benson*, the Court had rejected the notion that a patentable process had to involve the manipulation of matter in some way. See *Lundgren*, 2004 WL 3561262, at *4-*5 (quoting *Diehr*, 450 U.S. at 201 (Stevens, J., dissenting)).

Yet although the Board quoted further from Justice Stevens' summary of *Benson* in his dissenting opinion in *Diehr*,

those words went unheeded. In the relevant passage, Justice Stevens explained that

> the Court clearly held [in *Benson*] that new mathematical procedures that can be conducted in old computers, like mental processes and abstract intellectual concepts, see [409 U.S. at 67], are not patentable processes within the meaning of [35 U.S.C.] § 101.

That summary closely describes the patent in *State Street*. And the step of "implementing" an abstract incentive scheme in a business bears the same characteristics: an effort to use vaguely described, routine activity to secure a patent on an assertedly novel but wholly abstract idea. This Court has held that merely "implement[ing] a principle in some specific fashion" does not render a process patentable. *Flook*, 437 U.S. at 593. Simply using the word "implementing" can accomplish no more.

If the drafter of a patent may bring a mathematical algorithm "comfortably * * * within" the scope of patent protection simply by adding a token indication of use—"implementing the steps of the scheme" or "transferring compensation to said manager"—any mathematical algorithm can be patented. *Lundgren* firmly establishes the PTO's intention to continue issuing highly abstract business method patents.

It is no answer to say that any subject-matter errors by the PTO may be corrected in litigation challenging the validity of over-reaching patents. Not only is patent litigation notoriously expensive, see American Intellectual Property Law Association, *2005 Report of the Economic Survey* I-110, Table Q42f (reporting $5 million median cost for patent infringement suit with $25 million or more at stake), but a challenger to a patent's validity bears a heavy burden: "[A]ll patents are presumed valid." *Cardinal Chemical Co.* v. *Morton International, Inc.*, 508 U.S. 83, 93 n.15 (1993) (citing 35 U.S.C. § 282). Indeed, the Federal Circuit's appe-

tite for the patenting of abstract ideas makes that presumption nearly impossible to overcome where the flaw is ineligible subject matter.

IV. Abstract Business Method Patents Slow Innovation In The Financial Services Industry, Disrupt Its Participants, And Harm Consumers.

By allowing patentees to claim abstract ideas, the Federal Circuit and PTO are narrowing the public domain in areas of significant—and rapid—innovation. An overbroad patenting regime threatens innovation not only in the biological and medical sciences (as the present case demonstrates), but also in the financial services industry, another area vital to the Nation's economy.

A. Abstract Business Method Patents Hinder Innovation In The Financial Services Industry

Before *State Street*, innovation in the securities industry flourished without patent protection, generating between 1200 and 1800 new types of trade securities from 1980 to 2001. See, *e.g.*, Robert P. Merges, *The Uninvited Guest: Patents on Wall Street*, UC BERKELEY PUBLIC LAW RESEARCH PAPER NO. 126 at 7 (May 2003); see also W. Landes & R. Posner, THE ECONOMIC STRUCTURE OF INTELLECTUAL PROPERTY LAW 329 (2003) ("Despite the unavailability of business method patents until quite recently, there has been no shortage of marketing innovations."). Indeed, from the 1970s onward, this industry has brought forth a myriad of new products for investors. These advances include exchange-traded futures and options contracts on financial instruments (including equity options and Treasury futures); over-the-counter products linked to a variety of asset classes or indices (*e.g.*, equity derivatives, credit derivatives, currency and interest rate derivatives and inflation-linked products); and innovative forms of securities investments, including index-

linked securities, mortgage-backed securities, and securities backed by other assets.

Much of that innovation consists of imitation of, and incremental improvement on, new methods of investment and finance. Both the nature of business methods generally, and the transparency of American financial markets in particular, make it unlikely that effective methods will be long concealed: "Businesses are largely practiced in public." Rochelle Cooper Dreyfuss, *Are Business Method Patents Bad for Business?*, 16 SANTA CLARA COMPUTER & HIGH TECH. L.J. 263, 274 (2000).

> Accordingly, there is little need to especially encourage disclosure. Business methods are also hard to free ride on. They depend in strong ways on the social structure within the firms utilizing them—on compensation schemes, lines of reporting, supervising policies, and other business factors. * * * With lock in, network effects, and even good old fashioned loyalty, lead time (the first mover advantage) goes a long way to assuring returns adequate to recoup costs and earn substantial profit.

Id. at 274-75.

Because American financial markets are highly efficient, information travels quickly within them—and within the financial services industry. Product cycles are short—far shorter than the 20-year patent term—because innovation also spreads quickly. Indeed, competitors often adapt their own versions of new product ideas within weeks after the products' initial introduction into the market. Bankers and brokers constantly develop and refine investment products that their competitors duplicate, while adding variations to their offerings in efforts to improve their products and services. In short, methods of doing business develop through competition as the market ruthlessly wrings out inefficiency.

Not only do abstract business method patents provide few if any discernible benefits in financial services markets, but those patents have marked deleterious effects. The financial services industry is a natural target for abstract business method patents, as the setting of the *State Street* case underscores. The very stock-in-trade of the industry is the harnessing of mathematical concepts toward the development of new financial products, transaction strategies, and marketplaces. Business methods fundamentally differ "from the subject matter of most patent protection because 'they affect not just products in competition, but rather the competitive process itself.' "[5] In addition, high transaction volumes in the financial services industry mean that a small slice of each transaction can produce huge royalties—and enormous deadweight losses to consumers.

Further, the availability of abstract business method patents diverts business investment away from true innovation that benefits consumers to defensive actions that primarily benefit patent lawyers. Existing financial services firms are forced to accumulate portfolios of "defensive" business method patents so that they have bargaining chips available for future negotiations and litigation with competitors and other business method patent holders who have no business but the exploitation of patents on the businesses of others.

This Court long ago addressed the latter problem, albeit in a different technological context. The Court's words aptly describe the results of allowing abstract business method pat-

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[5] Brian P. Biddinger, Note, *Limiting the Business Method Patent: A Comparison and Proposed Alignment of European, Japanese and United States Patent Law*, 69 FORDHAM L. REV. 2523, 2545 (2001) (quoting an unpublished early version of Rochelle Cooper Dreyfuss, *State Street or Easy Street: Is Patenting Business Methods Good for Business?*, in U.S. INTELLECTUAL PROPERTY: LAW AND POLICY (Hugh Hansen ed., 2001)).

ents. That practice, especially as pursued by non-participants in the relevant industry,

> creates a class of speculative schemers who make it their business to watch the advancing wave of improvement, and gather its foam in the form of patented monopolies, which enable them to lay a heavy tax upon the industry of the country, without contributing anything to the real advancement of the arts. It embarrasses the honest pursuit of business with fears and apprehensions of concealed liens and unknown liabilities to lawsuits and vexatious accountings for profits made in good faith.

Atlantic Works, 107 U.S. at 200.

Finally, abstract business method patents restrict innovation by introducing market inefficiencies that competition cannot correct. A broad patent can lengthen product cycles, as the expenses of litigation or royalties deters firms from devoting resources to fields potentially covered by business method patents. And such a patent may allow a single firm to exclude all competitors from a field of investment (or to collect rents from those who want to compete).

The historical development of the financial services industry reflected the historic view of the federal courts that "an art" (or, in current statutory terminology, a "process," see *Diehr*, 450 U.S. at 182-183) "is not a mere abstraction." *Hotel Security Checking Co.* v. *Lorraine Co.*, 160 F. 467, 469 (2d Cir. 1908). As a consequence, "[a] system of transacting business disconnected from the means for carrying out the system is not, within the most liberal interpretation of the term, an art." *Ibid.* By resuscitating the contrary notion ninety years later, the Federal Circuit has upset settled industry expectations.

B. Abstract Business Method Patents Are Currently Disrupting The Financial Industry And Its Consumers.

Because *State Street* was decided only seven years ago, the full impact of the Federal Circuit's unprecedented expansion of the scope of patentable subject matter is unclear. Even so, some firms already have used abstract business method patents to try to monopolize—or collect monopoly rents on—vital national markets.

1. eSpeed Inc. brought patent infringement lawsuits against several securities trading firms for infringing a patent for an "Automated auction protocol processor." The asserted claims covered a method of managing auction trades. See, *e.g.*, *eSpeed, Inc.* v. *Brokertek USA, LLC*, Case No. 03-612 (D. Del. Dec. 5, 2005) (mem. order). Although Brokertek and the other defendants prevailed at trial on the ground that the patent was invalid for insufficient written description (*id.* at 3), the defense against the invalid patent lasted two and one-half years and cost millions of dollars. And that defense is not over yet. The appellate process has just begun and—if the present case is any indication—the Federal Circuit may impose a more forgiving view of the written description requirement.

In earlier litigation, eSpeed enforced a patent for an "Automated Futures Trading Exchange" against the Chicago Mercantile Exchange, the Chicago Board of Trade, and NYMEX. eSpeed originally was a defendant in the matter, but settled with the original plaintiff by "purchas[ing] the patent along with the right to act as plaintiff in the present litigation." *eSpeed, Inc.* v. *Bd. of Trade*, Case No. M8-85(SCH), 2002 WL 827099, at *2 (S.D.N.Y. May 1, 2002). eSpeed then extracted a reported $48 million in license fees by settling with the other defendants and reaching agreement with IntercontinentalExchange without filing suit. See Mary Schroeder, *CME, CBOT to Pay eSpeed $30M in Patent Dis-*

pute, Sec. Indus. News, Sept. 2, 2002; Press Release, eSpeed, Inc., *eSpeed and New York Mercantile Exchange Reach Settlement Agreement on Wagner Patent* (Dec. 22, 2003), *available at* http://www.espeed.com/articles/article20031222.htm. The net result imposed increased costs (and deadweight losses) on every trade on a major U.S. futures exchange.

2. Priceline.com holds patents claiming a method for administering a "Dutch auction" over the Internet. See U.S. Patent No. 5,794,207, col. 32, ll. 40-54 (Claim 1); see also Patent No. 5,797,127 ("Method, apparatus, and program for pricing, selling, and exercising options to purchase airline tickets"). But a Dutch Auction is a "business method" that the U.S. Treasury uses to sell hundreds of billions of dollars' worth of securities each year. As Judge Posner observed, "the new 'business method' patents create the potential for inventors of new methods of doing business to obtain enormous monopoly power (imagine if the first person to think up the auction had been able to patent it); such patents also create a reward greatly in excess of the cost of the invention." Richard A. Posner, *The Law & Economics of Intellectual Property*, Daedalus, Spring 2002, at 5.

3. The PTO has even issued patents on basic financial instruments. Patent No. 6,963,852, for a "System and method for creating a defined benefit pension plan funded with a variable life insurance policy and/or a variable annuity policy," is a glaring example. That patent claims, among other things (*id.* col. 17, ll. 54-67):

> A computer-implemented data-processing method for creating a qualified defined benefit pension plan funded using variable life insurance contracts, the method comprising:
>
> (a) entering, via at least one user interface, actuarial data used to create the qualified defined benefit pension plan;

(b) based on the actuarial data, electronically generating a variable life insurance policy;

(c) funding the qualified defined benefit pension plan using the variable life insurance policy;

(d) electronically generating a separate agreement that extra-contractually modifies the variable life insurance policy, wherein the plan includes the policy and the separate agreement; and

(e) providing a guaranty of the plan benefits using the plan's policy and separate agreement.

Because defined-benefits pension plans funded by variable life insurance policies or variable annuities have existed for years, the patent holder had many potential targets for patent infringement suits. He has sued both Nationwide Life Insurance Co. and Travelers Life & Annuity Co.; the insurers responded by seeking declaratory judgments of non-infringement and invalidity. See *Travelers Life & Annuity Co.* v. *Koresko*, No. 05-5862 (E.D. Pa. filed Nov. 8, 2005); *Nationwide Life Insurance Co.* v. *Koresko*, No. 05-2006 (S.D. Ohio filed Nov. 23, 2005). The insurers may well succeed but have been forced to litigate their right to use an established, well-known financial instrument.

4. Another patent, although not yet the subject of reported litigation, illustrates how the most established and fundamental investment ideas and practices may receive patent protection. Entitled "Method and system for enabling smaller investors to manage risk in a self-managed portfolio of assets/liabilities," the patent claims (among other things):

A computer-based method for enabling an individual investor to manage risk underlying an investment comprising the steps of:

a) creating a representative portfolio of assets/liabilities that have a correlation to the in-

vestment for which the individual investor desires to manage risk;

b) submitting the representative portfolio to a computer system over a communications link; and

c) analyzing the representative portfolio using a processor to determine a price to charge the user to insure the value of the representative portfolio at a predetermined level at a predetermined time.

U.S. Patent No. 6,360,210, col. 16, l. 65-col. 17, l. 9 (Claim 27). That claim amounts to the mental activities involved in the creation and analysis of an investment portfolio. That something so routine could be patented highlights a particular problem in the patenting process if abstract ideas can be patented. For a business process like this, the prior art that might establish that the invention was not novel does not exist in patents or scientific papers. Rather, the mental processes claimed here and in other business method patents derive from common practice in the business world or directly from common sense—two sources that are difficult if not impossible to identify, assess, and compare to a patent application. For that reason, abstract business methods, like mathematical formulae, should be treated as part of the prior art as a matter of law. See *Flook*, 437 U.S. at 594.

* * *

Before the Federal Circuit improperly expanded the scope of patent protection to include natural phenomena and abstract ideas, American financial markets thoroughly enabled efficient investment in innovation. This Court should restore the "delicate balance" (*Festo*, 535 U.S. at 730-31) that the Federal Circuit has upset. The need for reaffirmed guidance is especially acute in innovative sectors such as financial services where existing incentives for innovation are robust. Inventors should not be allowed to seize abstract ideas from the public.

V. By Reaffirming Its Precedents Requiring Patentable Processes To Be Physical And Material, This Court Can Forestall The Patenting Of Abstract Business Methods And Other Abstract Ideas.

The Federal Circuit has misinterpreted this Court's observation that the statutory subject matter of patent protection extends to "anything under the sun that is made by man" (*Chakrabarty*, 447 U.S. at 309) to mean that any ***insight*** or ***conclusion*** "made" by individuals may be patentable, whether or not that insight is part of a process that "makes" anything in the common-sense, tangible meaning of the word. To forestall the patenting of abstract ideas, the Court should reaffirm what it said in *Diehr* and many earlier decisions: that patentable processes must be ***physical*** and ***material*** because a "process" within the meaning of 35 U.S.C. § 101 "is a mode of treatment of certain ***materials*** to produce a given result." *Diehr*, 450 U.S. at 183 (emphasis added).

A. Requiring Patented Processes To Be Physical And Material Will Exclude Abstract Business Methods And Other Abstract Ideas.

This Court already has articulated the elements of an appropriate two-part analysis that would (1) exclude abstract ideas from the scope of patentability in the first instance, and (2) ensure that the addition of a vague and insubstantial step to an unpatentable idea would not succeed in securing a patent. This Court could end much patenting mischief simply by reaffirming that it meant what it said and enforcing the Federal Circuit's duty to comply with higher authority. See, *e.g.*, *Festo*, 535 U.S. at 724.

The Court has adhered to these standards from its early days. See *Flook*, 437 U.S. at 588 n.9 (noting that "[a]n argument can be made * * * that this Court has only recognized a process as within the statutory definition" if these requirements were satisfied). It is true that the Court in *Benson* declined to " hold that no process patent could ever qualify if it

did not meet the requirements of our prior precedents," 409 U.S. at 71, and that in *Flook*, 437 U.S. at 588 n.9, the Court assumed that the requirements were not exclusive. But the Court applied the test without apology in *Diehr*, and now—in light of the Federal Circuit's aggressive expansion of the subject-matter scope of patentable processes—has reached the point at which forthright, unambiguous guidance is necessary.

The Court's only alternative is to acquiesce in the Federal Circuit's limitless view. But that course would contravene this Court's precedents as well. The Court has recognized its duty to "proceed cautiously when [it is] asked to expand patent rights into areas wholly unforeseen by Congress." *Flook*, 437 U.S. at 596. Lacking a "clear and certain signal from Congress," *ibid.* (quoting *Deepsouth Packing Co.* v. *Laitram Corp.*, 406 U.S. 518, 5531 (1972)), that might confirm that the scope of patentable subject matter should be expanded, this Court should adhere to the clear dividing line expressed in its precedents. The proliferation of abstract business method patents should prompt the Court to make indisputably clear that the line is where *Diehr* left it.

First, this Court should confirm its identification in *Diehr* of the "clue to the patentability" of any process, whether or not it incorporates algorithms or other abstract principles. 450 U.S. at 184. To be patentable, the Court explained, a process must either (1) "include" a "particular machine" or (2) result in the "transformation" of a tangible "article" to a different state. *Ibid.* By its plain terms that formulation excludes interpersonal, societal, and financial methods and relationships as opposed to technological developments. *Cf.* European Patent Convention Art. 52(2)(c) (rendering "schemes, rules and methods for performing mental acts, playing games or doing business" unpatentable per se).

Second, and just as important, the Court should preclude the use of indefinite claims to embrace unpatentable subject

matter, for example by including some token step in addition to the expression or consideration of an abstract idea. As the Court has instructed, "a mathematical formula does not become patentable subject matter merely by including in the claim for the formula token postsolution activity." *Diehr*, 450 U.S. at 192 n.14; see also *id.* at 191-92 ("insignificant postsolution activity will not transform an unpatentable principle into a patentable process"). This "token" activity includes such steps as carrying out the calculation of an abstract formula on a non-novel computer system or "implementing" an abstract business scheme within an enterprise.

The principles underlying business methods are "basic tools" of commerce just as algorithms are "basic tools of scientific and technological work," and like algorithms, they should be "treated as though [they] were a familiar part of the prior art." *Flook*, 437 U.S. at 591-592. Each type of principle "reveals a relationship that has always existed." *Id.* at 593 n.15. As a consequence, just as with a patent incorporating a mathematical algorithm, the question for a patent including a business method should be whether, when the principle or insight underlying the business method "is assumed to be within the prior art, the application, as a whole, contains" a "patentable invention." *Id.* at 594.

Reaffirming the clear standards expressed in *Diehr* will prevent the Federal Circuit from impermissibly expanding the scope of patent protection until it swallows all branches of human activity. "Anything under the sun which is made by man" should mean just that: ***made***, not simply thought of.

B. Conversely, Allowing Patents For Abstract Business Methods Would Raise Serious Constitutional Doubts.

Another reason to reaffirm the subject-matter limitations recognized in *Diehr* is this Court's established practice of construing statutes to avoid "grave and doubtful constitutional questions." *Jones* v. *United States*, 529 U.S. 848, 849

(2000). The Constitution permits Congress to give "Inventors the exclusive Right to their * * * Discoveries" only "[t]o promote the Progress of Science and useful Arts." U.S. Const. Art. I, § 8. As this Court has recognized, the Framers intended the patent power as a narrow exception to the general common-law prohibition against monopolies in business:

> [T]he federal patent power * * * unlike the power often exercised in the sixteenth and seventeenth centuries by the English Crown, is limited to the promotion of advances in the 'useful arts.' It was written against the backdrop of the practices—eventually curtailed by the Statute of Monopolies—of the Crown in granting monopolies to court favorites in goods or businesses which had long before been enjoyed by the public.[6]

Graham v. *John Deere Co.*, 383 U.S. 1, 5 (1966) (internal citation and footnote omitted); see also Robert P. Merges, *The Proper Scope of the Copyright and Patent Power*, 37 HARVARD J. ON LEGIS. 45, 47-48 (2000).

The notion that an abstract method of doing business is an art or science under the Constitution is unlikely as an historical matter. The Framers considered and rejected a broader patent power which would have allowed Congress to "to establish public institutions, rewards, and immunities for the promotion of agriculture, commerce, and manufactures." Joseph Story, 3 COMMENTARIES ON THE CONSTITUTION OF THE UNITED STATES § 1150 (1833). Not content with the rejection of this proposal, several state ratifying conventions sought amendments prohibiting Congress from granting "exclusive advantages in ***commerce***" to anyone.[7] Allowing individuals

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[6] The Statute of Monopolies, 1623, Jam. 1, c. 3, outlawed all grants of monopoly *except* for patents covering "the sole Working or Making of any manner of new Manufactures." *Id.* § 6. See *United States* v. *Line Material Co.*, 333 U.S. 287, 330 n.10 (1948).

[7] *Ratification of the New Constitution by the Convention of the State of New York*, 4 AMERICAN MUSEUM 153, 156 (Philadelphia,

to obtain exclusive rights in the methods of commerce would have the same forbidden effect.

The Framers carved out the patent power as a special exception for monopolies to encourage innovation, but explicitly "limited" that power "to the promotion of advances in the 'useful arts.' " *Graham*, 383 U.S. at 5. They denied Congress the power to grant business monopolies. This Court should restore the balance that the Framers established and should construe the subject-matter limitations of the Patent Code to "avoid the constitutional question that would arise" (*Jones*, 529 U.S. at 858) if abstract methods of commerce were recognized as patentable processes.

* * *

Removing intellectual exercises, such as abstract business methods, from the scope of patentable subject matter benefits consumers by ensuring that strong competition in methods of analysis and means of providing services may continue without artificial restriction. The highly efficient and intensely innovative financial services markets in the United States should not be stifled by Federal Circuit decisions that depart from this Court's precedents and allow patentees to monopolize abstract methods and ideas.

Matthew Carey 1789) (emphasis added); *Remarks on the Amendments to the Federal Constitution Proposed by the Conventions of Massachusetts, New Hampshire, New York, Virginia, South and North Carolina, with the Minorities of Pennsylvania and Maryland by the Rev. Nicholas Collin, D.D.*, 6 AMERICAN MUSEUM 303, 303 (Philadelphia, Carey, Stewart & Co. 1789).

CONCLUSION

The judgment of the court of appeals should be reversed.

Respectfully submitted.

DONALD M. FALK
Counsel of Record
ERIC B. EVANS
Mayer, Brown, Rowe & Maw LLP
Two Palo Alto Square, Ste. 300
3000 El Camino Real
Palo Alto, CA 94306
(650) 331-2000

JEREMY GASTON
Mayer, Brown, Rowe & Maw LLP
700 Louisiana, Ste. 3600
Houston, TX 77002
(713) 221-1651

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Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS, D/B/A LABCORP,

Petitioner,

v.

METABOLITE LABORATORIES, INC. AND COMPETITIVE TECHNOLOGIES, INC.,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF *AMICUS CURIAE* FRANKLIN PIERCE LAW CENTER IN SUPPORT OF THE RESPONDENTS

CRAIG STEVEN JEPSON
Professor of Law
Counsel of Record

FRANKLIN PIERCE
LAW CENTER
2 White Street
Concord, NH 03301
(603) 228-1541

Amicus Curiae

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IN THE

Supreme Court of the United States

No. 04-607

LABORATORY CORPORATION OF AMERICA HOLDINGS, D/B/A LABCORP,

Petitioner,

v.

METABOLITE LABORATORIES, INC. AND COMPETITIVE TECHNOLOGIES, INC.,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF *AMICUS CURIAE* FRANKLIN PIERCE LAW CENTER IN SUPPORT OF THE RESPONDENTS

INTEREST OF *AMICUS CURIAE* [1]

Amicus curiae Franklin Pierce Law Center (hereafter "Pierce Law") is an accredited law school located in Concord, New Hampshire. From its

[1] Both parties have consented to the filing of this brief *amicus curiae*. The letters of consent have been filed with the Clerk of the Court. This brief was not authored, in whole or in part, by counsel to a party, and no monetary contribution to the preparation or submission of this brief was made by any person or entity other than the *amicus curiae*. *Amicus Curiae* gratefully acknowledges the assistance of law students C. Gideon Korrell and Sean Tassi.

founding in 1973, a principal mission of Pierce Law has been the teaching of patent law and practice. The sole interest of *Amicus Curiae* in this case is the proper development and application of patent law to promote innovation and economic progress.

DISCUSSION

A number of provisions in the Patent Laws limit the scope of an inventor's patent rights. The invention must be patentable subject matter, i.e. "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." 35 U.S.C. § 101 (2000); *see also Diamond* v. *Diehr*, 450 U.S. 175, 182 (1981) ("Congress intended statutory subject matter to 'include anything under the sun that is made by man.'") (expanding patentable processes to include computer-program related inventions). The invention must have demonstrable utility; the invention must be novel and nonobvious. 35 U.S.C. §§ 101-103 (2000).

In addition, the inventor must comply with certain formal requirements. The specification must include a written description of the invention sufficient to enable a person having ordinary skill in the art (hereafter "POSA") to which the patent is most closely related to make and use the invention. In addition, the inventor must disclose her best mode of practicing the invention, and must distinctly claim the subject matter of her invention. 35 U.S.C. § 112, ¶¶ 1, 2 (2000). Only after meeting these requirements does an inventor qualify for her

patent rights, and then only for a limited time. 35 U.S.C. § 154(a)(2) (2000).

While the question this Court presented for review does not facially challenge the standards for patentable subject matter, the invitation of this Court to the Solicitor General indicates an interest in considering whether the patent-in-suit claims patentable subject matter. The Solicitor General counseled denial of the petition for writ of certiorari and endorsed as correct the application by the PTO of this Court's standards articulated in *Diehr*.

Pierce Law agrees that the PTO correctly applied the standards for patentable subject matter set forth in *Diehr*. Pierce Law urges, however, that this case is the appropriate vehicle for building upon *Diehr* by discarding the judicially-created prohibition against patent claims directed to so-called laws of nature.

SUMMARY OF ARGUMENT

This Court should discard the prohibition against patent claims directed to so-called laws of nature. The prohibition arose from dicta contained in old, English, common law decisions. It has no statutory support in our law. It is unnecessary and nearly impossible to apply because it is error-prone, redundant, and obsolete.

This Court has never invalidated a patent claim for claiming a law of nature. This Court has, instead, correctly relied only on statutory authority mandated by Congress in 1952 under 35 U.S.C. §§ 102, 103, and 112.

Recent experience in the United States shows that when this Court, the Legislature, or the Executive has rejuvenated a component of our patent system, that action has rejuvenated a component of our economy.

The prohibition against claims directed to laws of nature is a relic, an arbitrary bar to patentability, such as Congress and this Court consistently have acted to eliminate.

ARGUMENT

Congress never intended patentability to turn on whether what is claimed might be considered a law of nature. Congress intended patentability to turn only on whether what is claimed, when viewed as a whole, meets the requirements of patentability as set forth in 35 U.S.C. §§ 101, 102, and 103.[2] The Committee Reports accompanying the 1952 Patent Act reveal that Congress intended statutory subject matter to "include anything under the sun that is made by man."[3] S. Rep. No. 82-1979, at 5 (1952); H.R. Rep. No. 82-1923, at 6 (1952). *See also* *Diamond* v. *Chakrabarty*, 447 U.S. 303, 315 (1980)

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[2] "The repetitive use of the expansive term 'any' in § 101 shows Congress's intent not to place any restrictions on the subject matter for which a patent may be obtained beyond those specifically recited in § 101." *State St. Bank & Trust Co.* v. *Signature Fin. Group, Inc.*, 149 F.3d 1368, 1373 (Fed. Cir. 1998) (Rich, J.).

[3] P. J. Frederico, a principal draftsman of the 1952 Patent Act, also employed this expansive language in his testimony regarding that legislation: "[U]nder section 101 a person may have invented a machine or a manufacture, which may include anything under the sun that is made by man * * *." *Patent Law Codification & Revision: Hearings on H.R. 3760 Before Subcomm. No. 3 of the House Comm. on the Judiciary*, 82d Cong. 37 (1951).

("Congress, not the courts, must define the limits of patentability"); *State St. Bank & Trust Co.*, 149 F.3d at 1374-75 (Rich, J.) (explaining that under the 1952 Patent Act, many once-held exclusions are no longer applicable).

This mandate reflects the role of the Constitution in protecting the rights of Citizens:

> The law acknowledges the existence of the right of an inventor to his invention as property, and the Constitution is remarkably exact in the language in which it speaks of this important subject. The Constitution does not attempt to give an inventor a right to his invention * * *. No such thing. But the Constitution *recognizes* an original, pre-existing, inherent right of property in the invention, and authorizes Congress to secure to inventors the enjoyment of that right. But the right existed before the Constitution and above the Constitution, and is, as a natural right, more clear than that which a man can assert in almost any other kind of property. * * * Invention, as a right of property, stands higher than inheritance or devise, because *it is personal earning*.

Argument by Daniel Webster for Charles Goodyear in the patent case *Charles Goodyear* v. *Horace H. Day*, United States Circuit Court for the District of New Jersey, March, 1852. (emphasis in original).[4]

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[4] Daniel Webster was born in Salisbury, N.H., January 18, 1782, attended Phillips Exeter Academy, Exeter, N.H., and in 1801 graduated from Dartmouth College, Hanover, N.H. The citizens of New Hampshire elected him as a Federalist to the Thirteenth and

I. THIS COURT HAS NEVER INVALIDATED A PATENT CLAIM FOR CLAIMING A LAW OF NATURE.

Because this Court has never invalidated a patent claim for being directed to a so-called law of nature, this Court should affirmatively discard the prohibition. Absent such direction, the lower courts will fail to embrace the broadest scope for patentable subject matter, as was mandated by Congress. Instead, courts will mistakenly continue to follow obiter dicta imported from English common law. That dicta has given rise to a false notion: That so-called laws of nature are unpatentable.

A. Birth of the Prohibition: The First Patent Claims to Laws of Nature Were Upheld.

This Court dates the prohibition against claiming laws of nature to *Le Roy* v. *Tatham* (*Le Roy I*), 55 U.S. (14 How.) 156 (1853). *See Diehr*, 450 U.S. at 185 (relying on *Le Roy*); *Chakrabarty*, 447 U.S. at 309 (relying on *Le Roy*); *Parker* v. *Flook*, 437 U.S. 584, 588-89 (1978) (relying on *Le Roy*); *Gottschalk* v. *Benson*, 409 U.S. 63, 67 (1972) (relying on *Le Roy*); *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948) (relying on *Le Roy*); *De Forest Radio Co.* v. *Gen. Elec. Co.*, 283 U.S. 664, 685 (1931) (relying on *Le Roy* for the

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Fourteenth Congresses (March 4, 1813-March 3, 1817). He represented Dartmouth College before this Court in *The Dartmouth College Case*, 17 U.S. (4 Wheat.) 518 (1819). *Webster, Daniel*, 12 Encyclopedia Britannica 549 (15th ed. 2005).

notion that scientific methods, not explanations, are patentable); *O'Reilly* v. *Morse*, 56 U.S. (15 How.) 62, 114-18 (1853) (citing *Le Roy* and English common law).

Tatham was the assignee of the Hanson patent for an improved method of manufacturing by extruding pipes from soft metals such as lead. *Le Roy I*, 55 U.S. at 172. The Hanson patent embodied the mechanics of an earlier invention patented in 1820. Hanson's invention, however, used a newly-discovered property in metals (that they may be recombined and strengthened when placed under extreme pressure) which resulted in a marked improvement in pipe manufacturing—wrought pipe rather than cast pipe. *Id.* at 174. This Court wrote that while natural "processes used to extract, modify, and concentrate natural agencies" are inventive, the patentable "invention is not in discovering them, but in applying them to useful objects." *Id.* at 175 ("A new property discovered in matter, when practically applied, in the construction of a useful article of commerce or manufacture, is patentable").

That discussion, however, was obiter dictum, as this Court wrote: "The question whether the newly developed property of lead * * * might have been patented, if claimed as developed * * * was not in the case." *Id.* at 177. Indeed, this Court ultimately upheld Hanson's patent while acknowledging that it was on a law of nature:

> 'A patent will be good, though the subject of the patent consists in the discovery of a great,

> general and most comprehensive principle in science or law of nature, if that principle is, by the specification, applied to any special purpose, so as thereby to effectuate a practical result and benefit not previously attained.'

Le Roy v. *Tatham* (*Le Roy II*), 63 U.S. (22 How.) 132, 135-36 (1860) (quoting *Household Coal & Iron Co.* v. *Neilson*, 1 Webs. Pat. Cas. 673, 683 (S.C.(H.L.) 1843) (also upholding a patent directed to a law of nature)).

In *Neilson*, James Beaumont Neilson's invention was the pre-heating of air before sending it into a blast furnace. Use of the invention increased the temperature of the fire in the blast furnace and the efficiency of iron smelting. *Neilson* v. *Harford*, 151 Eng. Rep. 1266 [1 Webs. Pat. Cas. 328] (Exch. 1841). No device was claimed, which raised the question of whether Neilson claimed a mere principle or instead a patentable process. The English court upheld the patent as directed to a patentable process. *Id.* at 1274. Thus, the foundation for the judicially created prohibition against patent claims directed to so-called laws of nature is at best obiter dictum.

A dictum that has not acquired a gloss in reason should not be followed. In *Cohens* v. *Va.*, 19 U.S. (6 Wheat.) 264 (1821), Chief Justice Marshall disapproved reliance on dicta:

> It is a maxim not to be disregarded, that general expressions, in every opinion, are to be taken in connection with the case in which those expressions are used. If they go beyond the

> case, they may be respected, but ought not to control the judgment in a subsequent suit when the very point is presented for decision. The reason of this maxim is obvious. The question actually before the Court is investigated with care and considered in its full extent. Other principles which may serve to illustrate it, are considered in their relation to the case decided, but their possible bearing on all other cases is seldom completely investigated.

Id. at 399-400.

Because the dictum from *Le Roy* "ought not to [have controlled] the judgment in [the] subsequent" cases, those cases on this point are entitled to little weight.

B. Many Decisions Purporting to Invalidate Patent Claims to Laws of Nature Do So Only by Importing Conditions of Patentability from Statutory Provisions.

Many decisions seen as turning on unpatentable subject matter have, on closer reading, turned on statutory criteria imported from 35 U.S.C. §§ 102, 103, or 112. *See Flook*, 437 U.S. at 600 (Stewart, J., dissenting). In these decisions, reliance on one or more of §§ 102, 103, or 112 to invalidate the patent claims would have been appropriate, but the reliance on unpatentable subject matter was misplaced.

An example is *Funk Bros. Seed Co.*, 333 U.S. at 127 (denying patentability as "natural

phenomenon" to man-made mixture of six isolated bacterium recombined in respective quantities so as to be noninhibitive of each other), which actually was decided on the basis of what would soon thereafter become known as 35 U.S.C. § 103 obviousness:

> There is, of course, an advantage in the combination. The farmer need not buy six different packages for six different crops. He can buy one package and use it for any or all of his crops of leguminous plants. And, as respondent says, the packages of mixed inoculants also hold advantages for the dealers and manufacturers * * * . But a product must be more than new and useful to be patented; it must also satisfy the requirements of invention or discovery.

Id. at 131.

Likewise, Judge Rich explicated in *State St. Bank & Trust Co.*, 149 F.3d at 1376, that all the decisions that had been thought to hold that business methods were not patentable subject matter were, on closer reading, based on statutory grounds (35 U.S.C. § 102 (novelty) or § 103 (obviousness)). The courts had blurred the subject matter requirement with those statutory requirements.

The blurring is understandable because in one sense, the prohibition against patent claims directed to so-called laws of nature is but an undeniable truism: At some level of abstraction the statutory requirements for patentability cannot be

met. *See In re Walter*, 618 F.2d 758, 769 (C.C.P.A. 1980) (Rich, J.) ("One could as easily say that the inclined paper-making wire in *Eibel Process Co.* [v. *Minn. & Ont. Paper Co.*, 261 U.S. 45 (1923)] was on a fundamental level, mathematical in nature because it operated according to the law of gravity * * * ."); *Katz* v. *Horni Signal Mfg. Corp.*, 145 F.2d 961, 961 (2d Cir. 1944) (J. Frank, J., A. Hand, & T. Swan, JJ.) ("Epoch-making 'discoveries' of 'mere' general scientific 'laws,' without more, cannot be patented."). Justice Story explained:

> A patent cannot be for a mere principle, properly so called; that is, for an elementary truth. But the word principle is often used in a more lax sense, to signify constituent parts, peculiar structure, or process; and in specifications, it is generally used in this latter sense; and in this view, it may well be the subject of a patent.

J. Story, *On the Patent Laws*, 16 U.S. (3 Wheat.) app. n. (ii) at 15-16 (1818). Thus, where courts have not clearly seen that claims should be rejected as not being novel and nonobvious, courts have resorted, mistakenly, to subject matter.

Therefore, the prohibition against claims directed to so-called laws of nature—in addition to being judicially created and founded in dicta—is unnecessary. The prohibition is also unworkable and contrary to sound economic policy.

II. SOUND POLICY SUPPORTS ISSUANCE OF CLAIMS DIRECTED TO LAWS OF NATURE.

We have learned much since 1955 when Judge Learned Hand testified on the American Patent System:

> You can find—I have been at the job nearly 50 years—there are two schools and the one school beats the air and says without the patent system the whole of American industry would never have developed. It is the stimulus which has brought us to the top, and the other says it is nothing but a beastly method * * * .
>
> No one really knows. Each side is beating the air.

American Patent System: Hearings on S. Res. 92 Before the Subcomm. On Patents, Trademarks, & Copyrights of the Comm. on the Judiciary, 84th Cong. 116 (1955).

We are beating the air no longer. Recent changes in laws related to patents prove that expanding the scope of subject matter protected by patents, rather than contracting it, fosters growth and innovation.

A. Reinvigorating Our Patent System Reinvigorated Our Economy.

The United States patent system was robust until the early part of the last century when the judiciary slowly soured on it:[5]

> There can be no doubt that the Act of 1952 [was] meant to change [that] slow but steady drift of judicial decision that had been hostile to patents which made it possible for Mr. Justice Jackson in dissent to speak of the 'strong passion in this Court for striking them' (patents) 'down so that the only patent that is valid is one which this Court has not been able to get its hands on.'

Reiner v. *I. Leon Co.*, 285 F.2d 501, 503 (2d Cir. 1960) (L. Hand, J.) (quoting *Jungerson* v. *Ostby & Barton Co.*, 335 U.S. 560, 572 (1949)). Unfortunately, the anti-patent hostility of the courts continued.[6]

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[5] "The importance of federal patent law during the nineteenth century can be measured not only in terms of the lawyers attracted to the field, but also in the treatment that the subject received at the Court." John F. Duffy, *The Festo Decision and the Return of the Supreme Court to the Bar of Patents*, 2002 Sup. Ct. Rev. 273, 274-75 (2002). In upholding Alexander Graham Bell's patents in the *Telephone Cases*, this Court consolidated five matters, heard oral argument over twelve days, and filed a report filling an entire volume of the U.S. Reports. *Id.* at 275. Particularly interested in patent law, Justice Story wrote a number of seminal opinions and articles that are still referred to today. *Id.* "And, even when the Court was drowning in appeals toward the end of the century, retiring Justice William Strong supported a congressional proposal that would have limited the Court's mandatory appellate jurisdiction except in patent and copyright cases." *Id.*

[6] *See* James W. Geriak, *Synergism—How Long Will the Malady Linger On?* 1980 Pat. L. Ann. 51 (1980) (discussing various

As our patent system weakened, our economy weakened. "[In] the 1970s, when productivity growth rates fell sharply" and in the 1980s, "when Japanese competition fostered the notion that U.S. manufacturing industries were on the decline," the bar, industry, and government mobilized. Nat'l Research Council of the Nat'l Acads., *A Patent System for the 21st Century* at 18 (Stephen A. Merrill, et al., eds. 2004). Consequently, "[t]he 1980s saw [an] upward surge in the role and importance of the patent system." 1 Donald S. Chisum, *Chisum on Patents* § 7 (2005). "Beginning in 1980 a series of legislative actions, judicial decisions, executive branch initiatives, and international agreements * * * strengthened the rights of intellectual property owners [by extending rights] into new areas of technology." *A Patent System for the 21st Century* at 21-22.[7]

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reincarnations of tests for patentability which have "clouded the minds of the courts"); *see also Flook*, 437 U.S. at 584 (1978) (claimed process lost status as patentable subject matter simply because one step in the process would not be patentable subject matter if considered in isolation.); *Sakraida* v. *Ag Pro, Inc.*, 425 U.S. 273 (1976) (disparaging patents to so-called "co· ıbinations"); *Brenner* v. *Manson*, 383 U.S. 519 (1966) (inventor must disclose in application a specific practical utility); *Republic Indus., Inc.* v. *Schlage Lock Co.*, 592 F.2d 963, 964-65 (7th Cir. 1979) ("Increasingly, the district courts in this circuit * * * have taken the view that synergism and not the criteria articulated in *Graham* v. *John Deere Co.*, 383 U.S. 1 (1966), is the controlling test in combination patent claims.").

[7] "The 'pro-patent' era is unquestionably associated with a rapid growth in the markets for new knowledge. On the basis of secondary data, Arora and colleagues [Arora, A., A. Fosfuri, and A. Gambardella, *Markets for Technology: Economics of Innovation and Corporate Strategy* (MIT Press 2001)] roughly estimate that the value of technology licensing in the United States increased from $24 billion in 1990 to $44 billion in 1995 in constant dollars, and the

Congress began the movement by enacting important, pro-patent legislation.[8] In 1982, Congress created the United States Court of Appeals for the Federal Circuit and gave it exclusive appellate jurisdiction over cases that arise under the patent laws. Federal Courts Improvement Act of 1982, Pub. L. No. 97-164, 96 Stat. 25 (codified as amended 28 U.S.C. § 1295(a)(1) (1995)). In 1984, Congress passed the Patent Law Amendments Act amending 35 U.S.C. §§ 103, 116, and 120, which changed the "complex body of case law [that discouraged] communication among members of research teams working in corporations, universities or other organizations." Patent Law Amendments Act of 1984, Pub. No. L. 98-622, § 104, 98 Stat. 3383 (codified as amended in scattered sections of 35 U.S.C. (1988)). Congress also amended the infringement statute at 35 U.S.C. § 271(f) to make an infringing act the exportation of

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number of deals increased from more than 200 to well over 2,100." *Id.* at 37. In addition, "Anand and Khanna [Anand, B. & T. Khanna, *The Structure of Licensing Contracts*, 48 J. Indus. Econ. 103, 135 (2000)] support the hypothesis of a direct relationship by showing that licensing is more frequent in industries where patents are also prevalent." *Id.*

[8] Important legislation facilitated moving university research to production lines and encouraged the commercial exploitation of federally funded research. *See* Fed. Tech. Transfer Act of 1986, Pub. L. No. 99-502, 100 Stat. 1785 (1986) (codified as amended at 15 U.S.C. § 3701 et seq. (1988)); Econ. Recovery Tax Act of 1981, Pub. L. No. 97-34, 95 Stat. 172, 241 (1981) (codified as amended at scattered sections of 26 U.S.C. (1984)); Bayh-Dole Act, Pub. L. No. 96-517, 94 Stat. 3015, 3019-28 (1980) (codified as amended at 35 U.S.C. §§ 200-212 (1984)); Stevenson-Wydler Technology Innovation Act of 1980, Pub. L. No. 96-480, 94 Stat. 2311 (1980) (codified as amended at 15 U.S.C. § 3701 et seq. (1984)).

components of a patented combination. Patent Law Amendments Act of 1984, Pub. L. No. 98-622, 98 Stat. 3383 (codified as amended in scattered sections of 35 U.S.C. (1988)). In 1988, Congress passed the Patent Misuse Reform Act, Pub. L. No. 100-703, 102 Stat. 4674, 4676 (codified as amended at 35 U.S.C. § 271(d) (1994)), restricting application of the misuse doctrine to certain patent licensing and sales practices. The same year, it enacted the Process Patent Amendments Act, Pub. L. No. 100-418, 102 Stat. 1107, 1563 (codified as amended at 35 U.S.C. § 271(g) (1994)), extending to owners of patents with claims directed to processes the right to exclude unauthorized importation of unpatented products made abroad by use of the claimed processes. 1 *Chisum on Patents* § 7 (enumerating important legislation that reinvigorated the economy).[9]

This Court followed Congress's lead, also expanding the subject matter protectable by patents. *Chakrabarty*, 447 U.S. at 318, upheld the patentability of genetically-altered living microorganisms. *Dawson Chem. Co.* v. *Rohm & Haas Co.*, 448 U.S. 176, 201 (1980), applied 35 U.S.C. § 271(d) to hold that the owner of a patent claiming a process of using an unpatented (and

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[9] Empirical research from 60 countries for the period 1960-1990 shows that the strength of patent protection is positively and significantly correlated with investment in research and development in modern economies. *See* Park, W. & J. Ginarte, *Intellectual Property Rights and Economic Growth*, 15 Contemp. Econ. Pol'y 51 (1997) (indexing the strength of patent protection in 60 countries to determine the role of intellectual property rights in economic growth).

unpatentable) herbicide had not misused the patent when he sold the herbicide but refused to license the process to competing manufacturers of the herbicide. This Court held that because the herbicide was not a staple suited for uses other than in the patented process, the patent owner was not unlawfully extending the scope of the patent claims. *Id.* at 201, 214 ("the provisions of § 271(d) effectively confer upon the patentee, as a lawful adjunct of his patent rights, a limited power to exclude others from competition in nonstaple goods."). Thus, this Court extended the subject matter protectable by patents.

Reinvigorating the patent system worked. "[By] the mid-1990s the [United States] economy was again exhibiting high productivity growth." *A Patent System for the 21st Century* at 18.

B. Expanding the Scope of Subject Matter Protectable by Patent-like Incentives Fosters Innovation.

By the early 1980s, twenty-five million Americans suffered from one or more of six thousand diseases so rare that they presented little economic incentive to drug innovators.[10] Therefore, to "provide [patent-like] incentives for drug companies to develop and manufacture products for rare diseases that would otherwise produce

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[10] Drug companies will not decide, *ex ante*, to risk capital on drug development unless there is a reasonable prospect of a substantial return. *See* Geoffrey Carr, *A Survey of the Pharmaceutical Industry: The Alchemists*, Economist, Feb. 21, 1998, at 4 of insert (reporting estimate of 13 years and 300 million dollars to develop a new drug).

insufficient patient demand to support drug development, Congress in 1983 enacted the Orphan Drug Act. See 21 U.S.C. 360aa-ee (1988)." Note, *FDA Reform and the European Medicines Evaluation Agency*, 108 Harv. L. Rev. 2009, 2013 n.24 (1995).[11] These patent-like incentives, which expanded the subject matter eligible for protection, fostered drug development.

In the ten years prior to enactment of the Orphan Drug Act ("ODA"), the FDA reports, only ten products for rare diseases were developed and approved for marketing without federal funding.[12] Since the passage of the ODA, however, the FDA has approved for market 283 orphan drugs and biologics. U.S. Food & Drug Admin., *List of Orphan Designations & Approvals*, http://www.fda.gov/orphan/designat/list.htm (last visited Jan. 31, 2006). The FDA also reports that more than 1,544 orphan designated products are in development. *Id.* Our enlightened expansion of the scope of protectable subject matter blazed a path for the rest of the developed world. *See Beyond Borders: The Global Biotechnology Report 2002*, at 107 (Ernst & Young 2002) ("Since introduction of

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[11] These provisions "allow tax credits for money spent on clinical testing of drugs for a 'rare disease or condition,' defined as one that affects fewer than 200,000 persons," as well as "drugs that are expected to cost more than they will earn on the market." *Id.* In addition, "the Act provides manufacturers with seven years of post-approval market exclusivity for any unpatentable orphan drug." *Id.*

[12] Frank R. Lichtenberg & Joel Waldfogel, *Does Misery Love Company? Evidence from pharmaceutical markets before and after the Orphan Drug Act*, NBER Working Paper No. 9750 (June 2003) *available at* http://papers.nber.org/papers/w9750.

the orphan drug rules by the EC in 2000, there have been over 150 applications submitted. Fourteen products achieved orphan drug status in 2000 and many more companies followed suit in 2001 * * * .").[13]

Pharmaceutical innovation also lagged in the field of neonatal and pediatric medicine until Congress put in place patent-like incentives that expanded the scope of protectable subject matter. Drugs cannot be used on children merely because they have been FDA approved for adults. Dosages and responses are not linear; the metabolism and the absorption rates for the body of a child are different than those of an adult. Despite the urgent need for pediatric applications, the lack of profitability for that small market precluded development of new drugs. As a result, the majority of all drugs approved for adult populations had not been approved, or adequately tested, for pediatric populations. Christopher-Paul Milne, *Exploring the Frontiers of Law and Science: FDAMA's Pediatric Studies Incentive*, 57 Food & Drug L.J. 491, 491-94 (2002).

In response to these realities, Congress decided to provide patent-like incentives to previously unpatentable subject matter in the Food & Drug Administration Modernization Act of 1997

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[13] "In the United States, the Bayh-Dole Act is credited with encouraging the creation of a whole generation of innovative startups from university research. It may be no coincidence that Japan's recent changes to its university system are designed to achieve precisely the same result." *Beyond Borders: Global Biotechnology Report 2005*, at 68 (Ernst & Young 2005).

("FDAMA"), Pub. L. No. 105-115, 111 Stat. 2296, 2305 (codified as amended at 21 U.S.C. § 355a (Supp. 1997)). FDAMA encourages pediatric testing by providing six months of market exclusivity for innovator drug sponsors who perform clinical studies on specific drugs for pediatric patients. *See* 21 U.S.C. § 355a(a) (2000).

The expansion of protectable subject matter succeeded. Prior to the enactment of the patent-like pediatric exclusivity provisions, only eleven of the seventy-one pediatric studies requested by the FDA were completed. *The Pediatric Exclusivity Provision: U.S. Food & Drug Admin. Jan. 2001 Status Report to Congress* at 8 (2001).[14] Over a six-year period between 1991 and 1996, drug sponsors agreed to complete seventy-one post-marketing pediatric studies, but then only eleven were actually completed. *Id.* All this changed with incentives.

The FDA reports that the "pediatric exclusivity provision has been highly effective for many drugs. In general, the industry's response has been vigorous and the public health benefits have been extensive." *Id.* Statistics from the FDA's website show that the patent-like incentives have significantly increased the number of drugs tested on pediatric patients. The FDA reports that drug sponsors had submitted 715 proposed study requests and the FDA had issued 311 written requests for studies as of December 2005. U.S. Food & Drug Admin. Ctr. for Drug Evaluation &

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[14] *Available at* http://www.fda.gov/cder/pediatric/reportcong01.pdf.

Research, *Pediatric Drug Development*, http://www.fda.gov/cder/pediatric/ (last visited Jan. 31, 2006). Additionally, 115 grants of pediatric market exclusivity had been obtained as of December 2005. *Id.*

Thus, recent history shows that changes to patent-related laws expanding the scope of subject matter eligible for patent protection and patent-like exclusivity have resulted in economic growth and a pouring forth of significant innovations.

III. THIS CASE IS THE APPROPRIATE VEHICLE FOR BUILDING ON *CHAKRABARTY* AND *DIEHR*.

The distinction between patentable subject matter, on the one hand, and a law of nature, on the other hand, has never shimmered with lucidity.[15] Consequently, the prohibition is difficult to apply, and such application leads to arbitrary and artificial line drawing and patent claim drafting gamesmanship. This Court should use the present case to build on *Chakrabarty* and *Diehr* by discarding the arbitrary and unworkable prohibition.

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[15] For example, electro-magnetic signals, when properly claimed, are patentable subject matter. *See Manual of Patent Examining Procedure* § 2106(B)(1)(c) (8th ed., Rev. Aug. 2005) ("However, a signal claim directed to a practical application of electromagnetic energy is statutory regardless of its transitory nature. *See O'Reilly*, 56 U.S. at 114-19; *In re Breslow*, 616 F.2d 516, 519-21, 205 USPQ 221, 225-26 (CCPA 1980)").

A. The Prohibition is Arbitrary and Has Always Been Difficult to Apply.

There is no bright line separating a patentable process from an unpatentable principle. Both are "[conceptions] of the mind, seen only by [their] effects when being executed or performed. Either may be the means of producing a useful result." *Tilghman* v. *Proctor*, 102 U.S. 707, 728 (1881); *see also Diehr*, 450 U.S. at 189 ("To accept the analysis proffered by the petitioner would, if carried to its extreme, make all inventions unpatentable because all inventions can be reduced to underlying principles of nature * * * ."); *Le Roy I*, 55 U.S. at 174 ("The word principle is used * * * with such want of precision in its application, as to mislead.").

This Court early on encountered the elusive distinction between a patentable new method and unpatentable known principles in two cases involving similar technology. *Dolbear* v. *Bell*, 126 U.S. 1 (1888), concerned only the scope of claims of the Bell patent of March 7, 1876:

> 5. The method of, and apparatus for, transmitting vocal or other sounds telegraphically, as herein described, by causing electrical undulations * * * .

Id. at 13-14. Yet, thirty-four years earlier, in *Morse*, 56 U.S. at 62, this Court seemed to have little trouble finding unpatentable subject matter in a similar claim in an application to Morse:

> [8.] * * * [T]he use of the motive power of electric or galvanic current * * * for making or

> printing intelligible characters, signs, or letters, at any distances * * * .

Id. at 107.

The distinction that made the *Bell* decision difficult, and the *Morse* decision less so, was not in any distinction between the similar subject matters, nor in the choice of claim language, but rather the scientific context. Galvanic current had been stored and discharged as early as 1790.[16] Experiments showed that such current could be transmitted by wire and that it could be used for communication. By 1819 or 1820, Hans Christian Oersted, a Danish philosopher, had discovered that a magnetic needle at a distance could be deflected by a galvanic current, and thus mark information.[17] In 1820, André Marie Ampère expressly stated that such a deflective needle could be used for telegraphing. *Smith* v. *Downing*, 22 F. Cas. 511, 512-13 (C.C.D. Mass. 1850). Indeed, "very soon after the discovery made by Oersted, it was believed by men of science that this newly-discovered power might be used to communicate intelligence to distant places." *Morse*, 56 U.S. at 94. Thus, this Court, in effect, resolved the *Bell*

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[16] In 1746, the Abbé Jean Antoine Nollet, who became professor of experimental physics at Navarre, "used wire made of iron to connect a row of Carthusian monks more than a kilometre long"; when he discharged a Leyden jar through the wire, "the white-robed monks reportedly leapt simultaneously into the air." *See Biological Sciences*, 14 Encyclopedia Britannica 1069, 1096 (15th ed. 2005); *Electricity and Magnetism*, 18 Encyclopedia Britannica 159, 189 (15th ed. 2005).

[17] Gilbert Shapiro, *A Skeleton in the Darkroom: Stories of Serendipity in Science*, pp. 37-38 (HarperCollins 1986).

and the *Morse* decisions not on the basis of claiming or not claiming a law of nature, but rather on the basis that what Bell claimed was novel, and that what Morse claimed was obvious. As explained by Justice Grier in dissent, as a practical matter, dodging a decision based on whether what was claimed was a law of nature was unavoidable; attempting to draw a distinction based on subject matter is often impossible and usually unnecessary.[18]

This court again struggled with the elusive distinction between a patentable process and an unpatentable principle in *Tilghman*, 102 U.S. at 707. The sole claim of Tilghman's patent was directed to "the manufacturing of fat acids and glycerin from fatty bodies by the action of water at a high temperature and pressure." *Id.* at 709 (quoting U.S. Pat. No. 11,766 (Oct. 3, 1854)). The issue salient there was whether Tilghman was entitled to a claim on his process generally (viewed from a high degree of abstraction), or whether he was entitled to only a subset process limited by "the particular device mentioned" in the patent specification. *Id.* at 718. That claimed process might have included limitations on the time, temperature, and pressure of each step, the

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[18] Justice Grier reviewed the stated policy rationales for prohibiting time-limited patent claims to laws of nature, and found those rationales lacking. He expressed concern that the line between patentable processes as opposed to unpatentable laws of nature was difficult to discern, and was better viewed as a prohibition on that which was known. In his view, the laws of England and the United States, in effect, permitted claims to laws of nature in general and would have allowed Morse's claim in particular. *Id.* at 130-35.

arrangement of tubing, and the composition of the reaction vessel, because all such parameters were nicely described in the specification. *Id.* at 721; *see also* U.S. Pat. No. 11,766 at page 2, 1st col. (issued Oct. 3, 1854). The more structural limitations and process parameters in the claim, the more the claim looks like a patentable process; the fewer structural limitations and process parameters, the more the claim looks like an unpatentable law of nature.

But again, the distinction was found not in the choice of claim language, but rather primarily the scientific context. Michel Eugène Chevreul[19] as early as 1813 had published his discovery of the law of nature that tallow consisted of a base of glycerin and fatty acids, specifically, stearic, margaric, and oleic acids. Chevreul in 1825 also patented a particular process using sulfuric acid to separate the glycerin from the fatty acids. *Id.* at 711. That process did not require preventing water under pressure from becoming steam. Analogously, this Court held that Tilghman too had discovered a law of nature, that the elements of neutral fats can be separated from each other by water. But this Court also held, while asserting that the line was difficult to draw, that Tilghman was entitled to claim as a process the practical application of performing that separation by "the action of water at a high temperature and pressure." *Id.* at 718, 730.

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[19] Chevreul also invented the red, orange, yellow, green, purple, blue-color wheel. M. E. Chevreul, *De la Loi du Contraste Simultané des Couleurs et de l'assortiment des Object Colorés* (Paris 1839).

Without knowing the backdrop of the developments from 1813 to 1853, it is unlikely that Tilghman's process could have been seen to be a process rather than a law of nature. Patentability should not be based on serendipity.

The line between a law of nature and patentable subject matter shimmers with no greater clarity today. "Paroxetine hemihydrate is not the first invention to blur the line between [the workings of a] natural process and [its result,] a synthetic product * * * ." *SmithKline Beecham Corp.* v. *Apotex Corp.*, 403 F.3d 1331, 1360 (Fed. Cir. 2005) (Gajarsa, J., concurring); *see also Pres. & Fellows of Harvard Coll.* v. *Can. (Comm'r of Patents)*, [2000] 4 F.C. 528 (struggling "to distinguish between human intervention and the laws of nature," and dismissing appeal from decision of Comm'r of Patents denying an application for a transgenic mouse) (nonpatentability was affirmed by the Supreme Ct. of Can. at *Pres. & Fellows of Harvard Coll.* v. *Can. (Comm'r of Patents)*, [2002] 4 S.C.R. 45). Yet, the Harvard mouse is patentable subject matter under U.S. law. *See* United States Patent No. 4,736,866 to Leder, Philip, and Stuart, Timothy A., for "Transgenic Non-Human Mammals" issued April 12, 1988 assigned to President & Fellows of Harvard College, Cambridge, Mass.

This arbitrary, error-prone, and unworkable prohibition should be discarded.

B. This Court and Congress Consistently Have Moved Away from Arbitrary Line Drawing Regarding Patentable Subject Matter.

Prior to *Diehr*, the line with respect to the patentability of proto-software inventions was drawn by whether the patent claim included a mathematical algorithm. If it did, then it did not claim patentable subject matter. *Gottschalk*, 409 U.S. at 71-72 ("The mathematical formula involved here has no substantial practical application except in connection with a digital computer [so] the patent would wholly pre-empt the mathematical formula and in practical effect would be a patent on the algorithm itself."). This Court in *Diehr* erased that arbitrarily drawn line. 450 U.S. at 187 ("a claim * * * does not become nonstatutory simply because it uses a mathematical formula").

Likewise, in *Chakrabarty*, 447 U.S. at 303, this Court rejected drawing a line at "living inventions" even though some argued that that line had been clearly drawn by *Funk Bros. Seed Co.*, 333 U.S. at 131 (denying patentability to man-made mixture of six isolated bacterium recombined in respective quantities so as to be noninhibitive of each other) and *Am. Fruit Growers, Inc.* v. *Brogdex Co.*, 283 U.S. 1, 12 (1931) (denying patentability to man-made fungus-resistant citrus because: "It remains a fresh orange, fit only for the same beneficial uses as theretofore.").

Congress also eliminated certain arbitrary lines in the 1952 recodification of the Patent Law.

Risdon Iron & Locomotive Works v. *Medart*, 158 U.S. 68 (1895), had come to stand for a prohibition on claims directed to functions of a machine. This Court there held unpatentable a process for manufacturing belt pulleys, holding that no patent could "be obtained for a process which involves nothing more than the operation of a piece of mechanism, or, in other words, for the function of a machine." *Id.* at 77. Congress effectively erased that arbitrary distinction in the 1952 Patent Act by the broad inclusive language of § 101. *See In re Tarczy-Hornoch*, 397 F.2d 856, 867 (C.C.P.A. 1968) (Rich, J.) ("Exceptional treatment for this narrow class of processes is, pro tanto, inconsistent with the broad goal of the patent system * * * .").[20]

It was once believed that patentable weight could be given to printed materials only when a novel relationship was established between that printed material and the remaining structure of the claimed device or process. *See In re Miller*, 418 F.2d 1392, 1395 (C.C.P.A. 1969) (drawing line between patentable and nonpatentable subject matter). The Federal Circuit has since held that there is no support in 35 U.S.C. § 101 of the 1952 Patent Act for any such prohibition. *In re Gulack*, 703 F.2d 1381, 1384 (Fed. Cir. 1983) ("we do not interpret the board as holding that the printed matter can be ignored because it, by itself, is non-statutory subject matter"; if there is a basis for a

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[20] Decisions of the Court of Customs and Patent Appeals are binding as precedent on the United States Court of Appeals for the Federal Circuit. *South Corp.* v. *U.S.*, 690 F. 2d 1368, 1371 (Fed. Cir. 1982).

"printed matter" rejection, it is obviousness under § 103).

Most recently, the courts have recognized that Congress intended by § 101 that no arbitrary line may be drawn to prohibit claims to methods of doing business. In the seminal decision, Judge Rich quoted the rationale from a dissent by Judge Newman in *In re Schrader*, 22 F.3d 290, 298 (Fed. Cir. 1994):

> '[The business method exception] is * * * an unwarranted encumbrance to the definition of statutory subject matter in section 101, that [should] be discarded as error-prone, redundant, and obsolete. It merits retirement from the glossary of section 101. * * * All of the 'doing business' cases could have been decided using the clearer concepts of Title 35 [meaning §§ 102, 103, and 112].'

State St. Bank & Trust Co., 149 F.3d at 1375.

Because the arbitrary prohibition against patent claims directed to so-called laws of nature was borne of dicta, is contrary to the expansive language of § 101, and likewise is error-prone, redundant, and obsolete, it should be discarded.

CONCLUSION

For the reasons presented above, this Court should either affirm without reaching the issue of patentable subject matter, or, in the alternative, hold the arbitrary prohibition against the patentability of so-called laws of nature overruled.

Respectfully submitted,

CRAIG STEVEN JEPSON
Professor of Law
Counsel of Record

FRANKLIN PIERCE
LAW CENTER
2 White Street
Concord, NH 03301
(603) 228-1541

Amicus Curiae

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IN THE

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LABORATORY CORP. OF AMERICA HOLDINGS
Petitioner,

v.

METABOLITE LABORATORIES, INC., *et al.*
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF *AMICUS CURIAE* INTELLECTUAL PROPERTY OWNERS ASSOCIATION IN SUPPORT OF NEITHER PARTY

Of Counsel:

J. JEFFREY HAWLEY
President
DOUGLAS K. NORMAN
Chair, Amicus Brief Committee
INTELLECTUAL PROPERTY
OWNERS ASSOCIATION
1255 Twenty-Third Street, N.W.
Suite 200
Washington, DC 20037
(202) 466-2396

PAUL H. BERGHOFF
(Counsel of Record)
JOSHUA R. RICH
DENNIS D. CROUCH
MCDONNELL BOEHNEN
HULBERT & BERGHOFF LLP
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001

Counsel for Amicus Curiae

WILSON-EPES PRINTING CO., INC. – (202) 789-0096 – WASHINGTON, D. C. 20001

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BRIEF OF *AMICUS CURIAE* INTELLECTUAL PROPERTY OWNERS ASSOCIATION IN SUPPORT OF NEITHER PARTY

INTEREST OF *AMICUS CURIAE* [1]

Amicus curiae Intellectual Property Owners Association ("IPO") is a nonprofit, national organization of about 120 large and midsize companies and more than 250 small busi-

[1] The parties have consented to the filing of this brief *amicus curiae*. The letters of consent have been filed with the Clerk of the Court. In accordance with Supreme Court Rule 37.6, *amicus curiae* states that this brief was not authored, in whole or in part, by counsel to a party, and that no monetary contribution to the preparation or submission of this brief was made by any person or entity other than the *amicus curiae* or its counsel.

nesses, universities, inventors, authors, executives, and attorneys who are interested in patents, trademarks, copyrights, and other intellectual property rights. Founded in 1972, IPO represents the interests of all owners of intellectual property. IPO members receive about thirty percent of the patents issued by the Patent and Trademark Office to U.S. nationals. IPO regularly represents the interests of its members before Congress and the Patent and Trademark Office ("PTO"), and has filed *amicus curiae* briefs in this Court and other courts on significant issues of intellectual property law. The members of IPO's Board of Directors, which approved the filing of this brief, are listed in the Appendix.

IPO expressly declines to take any position on whether there is a factual or legal basis for finding Respondent's patent invalid or unenforceable.

IPO's interest in this case arises from the indication that this case may be used as a vehicle for limiting the type of innovations eligible for patent protection under 35 U.S.C. § 101. IPO believes that the bounds of patentable subject matter, as delineated by the Patent Act and by *Diamond v. Diehr*, 450 U.S. 175 (1981), are both correct and clear. Any narrowing of these bounds would likely disturb the existing property rights of patentees and disrupt incentives for current and future scientific and technological research.

DISCUSSION

There are a number of provisions in the current patent laws that serve to limit the scope of patent rights granted by the Government. First, an invention must fall within the scope of the subject matter established as patentable by the Patent Act, defined as "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof."[2] Second, the invention must have

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[2] 35 U.S.C. 101.

demonstrable specific utility,[3] be novel,[4] and constitute a non-obvious change from what was done before.[5] Third, the inventor must provide a written description of the invention sufficient to enable a person to make and use the invention, must disclose the best mode of practicing the invention, and must distinctly claim the subject matter of the invention.[6] Only in exchange for meeting all of those requirements does an inventor obtain patent rights, and then only for a limited time.[7]

Among these requirements, the scope of allowable subject matter is generally the easiest hurdle to surmount, as is warranted by the broad language of the Patent Act itself ("any new and useful process . . .") and by this Court's precedent. *Diamond v. Diehr*, 450 U.S. 175, 182 (1981) (noting that "Congress intended statutory subject matter to 'include anything under the sun that is made by man.'"). There are limits on patentable subject matter, however; as the *Diehr* court recognized, "laws of nature, natural phenomena, and abstract ideas" are "[e]xcluded from such patent protection." *Id.* at 185.

The question presented for review in this case does not, on its face, challenge the current standards for patentable subject matter. However, in its invitation to the Acting Solicitor General to express the views of the United States in this case, the Court indicated an interest in considering whether the patent-in-suit claimed patentable subject matter. That inquiry required consideration of *Diehr* and the scope of patentable

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[3] *Brenner v. Manson*, 383 U.S. 519 (1966).

[4] 35 U.S.C. § 102.

[5] 35 U.S.C. § 103(a).

[6] 35 U.S.C. § 112.

[7] 35 U.S.C. § 154(a)(2) ("such grant shall be for a term . . . ending 20 years from the date on which the application for the patent was filed in the United States.").

subject matter. The Solicitor General counseled denial of the petition for writ of certiorari and endorsed the PTO's application of the *Diehr* standards to determine the scope of patentable subject matter.

IPO believes that the current standards for patentable subject matter, as set forth by the Court in *Diehr*, correctly delineate between those innovations that should be eligible for patent protection and those that should not. Accordingly, IPO believes that this case should not serve as a vehicle for overturning or altering those standards. Rather, this case should reinforce the standards of *Diehr* and thus, support the expectation that innovations in yet unknown areas of technology will be eligible for patent protection.

SUMMARY OF ARGUMENT

The standards for determining whether an innovation constitutes patentable subject matter have been correctly enumerated by this Court's precedent. The language of the Patent Act along with cases such as *Diehr* and *Chakrabarty* support patent rights in virtually every area of research or development. For several reasons, this broad scope of patentable subject matter best "promote[s] the progress" in the useful arts.

First, the broad scope of subject matter eligibility properly places research and development decision-making into the hands of individuals and private entities. The U.S. patent system is primarily an economic tool for providing incentives that promote innovation. However, by its very nature, the course of innovation is unpredictable. Through countless unexpected leaps, the state of the art in many fields of science and technology is vastly different from that of twenty-five years ago when *Diehr* was decided, and the next twenty-five years will likely continue or accelerate the rapid development of new technologies. Limiting the scope of patentable subject matter for certain areas would change this natural course of

development by attenuating the incentive to innovate. IPO believes that an open technological playing field with broad patent eligibility is the best approach in a free market system. Cases may arise where the government hopes to either encourage or discourage innovation in a particular subject matter. Those cases, however, are best left to Congress.[8]

Second, the pace and unpredictability of innovation in science and technology hinders any nuanced control over the scope of patentable subject matter. Piecemeal limitations on patent eligibility, such as a *pro forma* technologic requirement or an expansion of the "natural phenomena" exception, would simply raise further questions as the art advances. Only a broad scope of eligibility settles the law and leaves the landscape clear for maximum innovation.

Third, even without a subject matter requirement, a patent may not recapture art already in the public domain—including unrecognized natural phenomena, mathematical formulas, and laws of nature. The Patent Act provides that a patentable invention must be new, novel, and nonobvious and must be described sufficiently to enable one of ordinary skill in the art to practice the invention. Under the well-established doctrine of inherency, even a natural phenomenon, mathematical formula, or law of nature that was unknown at the time a patent application was filed may serve as prior art against the invention. The availability of these requirements as additional gatekeepers for patent rights over natural phenomena and

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[8] For over fifty years, Congress has chosen to maintain a broad scope of patentable subject matter, described as "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." 35 U.S.C. § 101. *See also*, Rebecca Eisenberg, *Analyze This: A Law and Economics Agenda for the Patent System*, 53 Vand. L. Rev. 2081, n. 13 (2000) (noting that, in the wake of a judicial recognition of "business method" patents, Congress enacted new legislation that addressed and "arguably endorsed" the subject matter eligibility).

laws of nature further warrants against narrowing the eligibility requirements of 35 U.S.C. § 101.

ARGUMENT

I. THE COURT'S PRECEDENT ALREADY PROPERLY IDENTIFIES THE LIMITS OF PATENTABLE SUBJECT MATTER UNDER 35 U.S.C. § 101.

In several cases, the Court has discussed the scope of patentable subject matter; IPO asserts that those decisions correctly identify the limits of patentable inventions. The existing limits efficiently promote innovation in many different fields, avoid unnecessary judicial entanglement, and allow other provisions of the Patent Act to serve as clear gatekeepers for patentability. A narrowing of the current scope of patentable subject matter would threaten all of those benefits.

Section 101 of the Patent Act identifies "Inventions patentable" and serves as the initial patentability threshold. 35 U.S.C. § 101. The "broad language" of §101 provides for the patenting of processes, machines, articles of manufacture, and compositions of matter. *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980); *Diamond v. Diehr*, 450 U.S. 175, 182-83 (1981). In *Chakrabarty*, the Court acknowledged that "Congress plainly contemplated that the patent laws be given wide scope." 447 U.S. at 308. Although the Patent Act does not have any express exclusions from statutory subject matter, the Court has recognized a list of exceptions to the scope of patentable subject matter, in particular, "laws of nature, natural phenomena, and abstract ideas." *Diehr*, 450 U.S. at 185. In determining whether process claims that do not involve particular machines are patentable subject matter, transformation of an article "'to a different state or thing' is the clue to patentability." *Id.* at 184; *Gottschalk v. Benson*, 409 U.S. 63, 70 (1972).

In its brief as *amicus curiae*, the United States provided a clear outline of the rules for eligibility as patentable subject matter. *Brief of the United States as Amicus Curiae* at 5-9. In addition, the United States outlined several reasons for not using this case to alter the scope of eligibility.[9] IPO provides three further reasons why the current scope of eligibility should not be altered.

A. The broad scope of subject matter eligibility promotes a free market approach that best allocates research and development resources without judicial entanglement.

The primary underlying premise of a market economy is that relying on the market forces or "invisible hand" of supply and demand leads to greater efficiency and wealth. *See* Adam Smith, *The Wealth of Nations*, Book I (R.H. Campbell et al. eds., Clarendon Press 1976). At its core, the patent system is an economic tool that creates a strong market force—an incentive to innovate. That is, in exchange for a limited grant of exclusivity to practice his or her invention, the patentee agrees to publicly disclose that invention.

The current broad scope of subject matter eligible for patent protection allows the patent system to serve as an incentive to pursue any of a great range of potentially patentable lines of research, with each line competing for scarce resources and funding. A narrowing of patentable subject matter would cut off some of those lines and cause a reallocation of resources to other fields. The resulting system "would reduce the diversity of patentable innovation and restrict the wealth-generating potential of the patent system with artifi-

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[9] Specifically, the Government noted that (a) the record is not sufficiently developed to permit comprehensive consideration of subject matter eligibility requirements and (b) a decision narrowing eligibility requirements would undermine settled expectations and call into question a substantial number of patent claims. IPO agrees with both of these points.

cial limits on efficient market solutions." Erik Maurer, *An Economic Justification for a Broad Interpretation of Patentable Subject Matter*, 95 Nw. U. L. Rev. 1057, 1905 (2001). An open technological playing field with broad patent eligibility is the best approach in a free market system to maximizing wealth; further narrowing patent protection to certain subject matter areas would artificially limit the incentive to innovate in those areas and thus restrict market efficiency.

Broad eligibility for patentability is vital because innovation, by its very nature, is unpredictable and leads to nonobvious results. Fifty years ago, neither software stored in computer memory nor genetically modified organisms were considered patentable subject matter. But of course, these new areas of technology had barely been conceived fifty years ago. As technology advanced, attempts to secure patents for inventions of these types met resistance in the form of a high eligible subject matter barrier. That is, then existing law led to "crises in eligibility" that regularly appeared when new forms of technology became popular. Eileen Kane, *Splitting the Gene: DNA Patents and the Genetic Code*, 71 Tenn. L. Rev. 707 (2004). The crises arose because the new technologies did not fit well within the then-existing standards for eligibility. For instance, *Diehr* and *Chakrabarty* were both cases involving new technology whose patent eligibility was opposed by the PTO. *Diehr*, 450 U.S. at 181; *Chakrabarty*, 447 U.S. at 306-07. Prior inventors were likely directed to other technological fields because they anticipated that they could not reap the economic benefit of innovation. Today, businesses developing technologies from the fields involved in those cases, computer-controlled operations and biotechnology, are substantial engines driving the growth of the American economy. However, their success relies heavily on protection of their intellectual property rights—rights that would not have existed under a narrower interpretation of subject matter eligibility.

The next breakthrough technology area is unknown—perhaps it has not yet been conceived. One thing is certain, however. If no patent rights are available to protect innovation in that area, investment dollars and inventors will be directed elsewhere economically. Providing an open technological playing field with full access to patent rights, regardless of the subject matter, is the best approach to ensure success in a free market system and to avoid creating disincentives against the very type of innovation that leads to landmark breakthroughs.

In some cases, there may be good reason for the government to either encourage or discourage innovation in a particular subject matter. For instance, the government may want to encourage the development of childhood vaccines or the discovery of a better method of detecting explosives hidden within luggage. Various incentives such as government grants, patent extensions, and even patent prizes have been discussed as means for stimulating research. *See, e.g.*, Michael Abramowicz, *Perfecting Patent Prizes*, 56 Vand. L. Rev. 115 (2003). All of these situations, however, are best handled by Congress and the legislative process.

B. The rapid pace and unpredictability of innovation in science and technology hinders any nuanced judicial control over the scope of patentable subject matter.

Science and technology—"the useful arts" identified in the Constitution as potential subjects for a patent system—are progressing at a blistering pace. U.S. Const., art. I, § 8, Cl. 8. Every day, hundreds of innovations, both large and small, are conceived and the downstream processes of development and patenting are begun. As entirely new areas of technology develop at an ever increasing rate, the law must remain flexible to accommodate such pace and unpredictability—making

any nuanced control over the scope of patentable subject matter difficult at best.

Piecemeal limitations on patent eligibility, such as a specific technological arts requirement or an expansion of the "natural phenomena" exception, would simply raise further questions as the art advances. Exceptions to the notion of patentable broad subject matter would likely be challenged by patentees in the PTO and in court and would create an atmosphere of uncertainty that would necessarily chill innovation.

For example, after the decision in *State Street Bank & Trust Co. v. Signature Financial Group, Inc.*, 149 F.3d 1368 (Fed. Cir. 1998), PTO examiners were instructed to reject method claims under § 101 if the claims did not include a clear link to the "technological arts." Over time, any functional aspect of the requirement was lost and all that remained was a formalistic test that could be passed by merely reciting that a step of the questioned claim operated "through a computer." *See Ex parte Lundgren*, 76 U.S.P.Q.2d 1385 (Bd. Pat. App.& Int. 2005). In *Lundgren*, the PTO's Board of Patent Appeals and Interferences finally eliminated the technological arts test, finding "no judicially recognized separate "technological arts" test to determine patent eligible subject matter under § 101." The PTO concluded, as IPO urges here, that limiting the scope of eligibility created an artificial barrier to claiming inventions.

Similarly, numerous inventions today use newly-discovered principles. Currently, inventors can direct their research to make sure they can take economic advantage of their work. An expansion of the "natural phenomena" exception might cause such inventors to avoid disclosing the fruits of their labors or protecting them through trade secret protection. Neither of those approaches adds to the storehouse of knowledge from which others can draw to conceive further inventions. IPO believes that only a broad range of eligibility

within the scope of § 101 will settle the law in a manner beneficial to the public.

C. Strong requirements of novelty, nonobviousness, and description protect against overreaching patents and warrant against further restricting patentability based on subject matter.

One of the concerns often expressed with regard to the scope of patentable subject matter is that patents will issue that allow a monopoly on knowledge that existed independent of any invention. No one wants such overreaching or overbroad patents, and the prevention of those inappropriate patents is certainly within the purview of the Court. However, there is no cause for alarm merely because subject matter is patentable. Even without the subject matter eligibility requirements, statutory language of the Patent Act provides strong protections against attempts to obtain overreaching claims or claims directed to natural phenomena, mathematical formulas or laws of nature. Specifically, such claims must be new, nonobvious, and described sufficiently to satisfy the requirements of 35 U.S.C. § 112. As such, fears of patents directed to these areas are not well-founded and do not require any expansion of the exceptions to patentable subject matter eligibility.

It is a fundamental premise of the patent system that inventions already in the public domain may not be recaptured in a later patent application.[10] If publicly known, natural phenomena, mathematical formulas, or laws of nature would certainly serve as prior art against any patent application claiming rights thereto. Further, under the doctrine of inherency, a

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[10] Under 35 U.S.C. §102(b), a one-year grace period prevents an inventor from capitalizing on an invention for more than one year prior to filing his or her patent application.

natural phenomenon, mathematical formula, or law of nature that was unknown at the time a patent application was filed may nevertheless serve as prior art against the invention. *See In re Cruciferous Sprout Litig.*, 301 F.3d 1343 (Fed. Cir. 2002). That is, the Court established over fifty years ago that natural phenomena and laws of nature are part of the "storehouse of knowledge of all men," regardless of whether those phenomena or laws were previously discovered.

> The qualities of these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men. They are manifestations of laws of nature, free to all men and reserved exclusively to none. He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes.

Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 130 (1948).

Furthermore, an inventor must provide a written description of his or her invention. That description must enable one of ordinary skill in the art to practice the full scope of the invention, a requirement that would be difficult (if not impossible) to meet if an inventor sought to cover all uses of natural phenomena or laws of nature. By strictly enforcing all of the requirements of 35 U.S.C. § 112, the PTO can avoid any need to constrict § 101.

These requirements for patentability under 35 U.S.C. §§ 102, 103(a), and 112 further warrant against narrowing the eligibility requirements of 35 U.S.C. § 101.

CONCLUSION

IPO believes that the standards of patentable subject matter eligibility are correctly delineated by the Patent Act and *Diehr*. IPO further believes that this case should not serve as a vehicle for creating further limitations that might disrupt those standards.

Respectfully submitted,

Of Counsel:

J. JEFFREY HAWLEY
President
DOUGLAS K. NORMAN
Chair, Amicus Brief Committee
INTELLECTUAL PROPERTY
OWNERS ASSOCIATION
1255 Twenty-Third Street, N.W.
Suite 200
Washington, DC 20037
(202) 466-2396

PAUL H. BERGHOFF
(*Counsel of Record*)
JOSHUA R. RICH
DENNIS D. CROUCH
MCDONNELL BOEHNEN
HULBERT & BERGHOFF LLP
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001

Counsel for Amicus Curiae

APPENDIX

Members of the Board of Directors,
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JP Morgan Chase & Co.

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J. Jeffrey Hawley
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Robert P. Hayter
United Technologies
Corp.

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Micron Technology, Inc.

John K. Williamson
Kirkpatrick & Lockhart Nicholson Graham LLP

Jon D. Wood
Bridgestone Americas Holding, Inc.

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LABORATORY CORPORATION OF AMERICA HOLDINGS, dba LabCorp,

Petitioner,

v.

METABOLITE LABORATORIES, INC., *et al.*,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF INTERNATIONAL BUSINESS MACHINES CORPORATION AS AMICUS CURIAE IN SUPPORT OF NEITHER PARTY

DAVID J. KAPPOS
IBM CORPORATION
One North Castle Drive
Armonk, NY 10504
(914) 765-4343

PAIK SABER
IBM CORPORATION
650 Harry Road
San Jose, CA 95120
(408) 927-3390

CHRISTOPHER A. HUGHES
Counsel of Record
MORGAN & FINNEGAN, L.L.P.
3 World Financial Center
New York, NY 10281
(212) 415-8700

JOHN R. THOMAS
GEORGETOWN UNIVERSITY
LAW CENTER
600 New Jersey Avenue, NW
Washington, DC 20001
(202) 662-9000

Counsel for Amicus Curiae
International Business Machines Corporation

December 23, 2005

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BRIEF OF INTERNATIONAL BUSINESS MACHINES CORPORATION AS AMICUS CURIAE IN SUPPORT OF NEITHER PARTY[1]

International Business Machines Corporation (IBM) respectfully submits this brief as *amicus curiae* in support of neither party.

INTEREST OF AMICUS CURIAE

IBM is a globally recognized leader in the field of information technology research, development, design, manufacturing, and related services. During IBM's nearly 100-year history, its employees have included five Nobel laureates, five National Medal of Science recipients, and eight winners of the National Medal of Technology. The United States Patent and Trademark Office (USPTO) has granted IBM tens of thousands of United States patents, including more patents than any other corporate assignee for the past twelve years. IBM is the proprietor of more patents claiming computer-related inventions than any other entity in the world. IBM is also ranked in the top two for patents issued on business methods, as classified by the USPTO.[2] IBM believes it can provide a balanced view on important issues implicated by this case — namely, the patentability standard under 35 U.S.C. § 101, and particularly as it relates to patenting of business methods.

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[1] In accordance with Supreme Court Rule 37.6, Amicus states that this brief was authored in its entirety by the counsel listed herein. No person or entity other than Amicus listed on the cover made a monetary contribution to the preparation or submission of this brief. Letters reflecting written consent of the parties to the submission of this brief have been filed with the Clerk of the Court.

[2] According to information available to IBM, it has been issued 308 patents on business methods as of December 13, 2005.

As a leading recipient, licensee, and licensor of patents, amicus IBM is committed to maintaining the integrity of the United States patent laws. IBM is particularly interested in assuring that the statutory standard (35 U.S.C. § 101) for patent eligibility of business methods is addressed in a manner that is both rational and consistent with established principles of patent law.

INTRODUCTION AND SUMMARY OF ARGUMENT

Since this Court last interpreted section 101 of the patent statute, *see Diamond v. Diehr*, 450 U.S. 175, 191-93 (1981), certain decisions of the Federal Circuit Court of Appeals have broadened the scope of subject matter deemed eligible for patenting, particularly in the area of business methods. Under the standard currently followed by the Federal Circuit, an invention is eligible for patenting if "it merely achieves a useful, concrete, and tangible result." *State Street Bank & Trust Co. v. Signature Fin. Group, Inc.*, 149 F.3d 1368, 1373 (Fed. Cir. 1998). Under this lenient standard, the section 101 inquiry has taken an "end-justifies-the-means" approach, which has resulted in patents arising from a diverse range of human behavior traditionally outside the realm of patent protection, including economic analyses, artistic techniques, athletic skills, and abstract methods of doing business. As one Federal Circuit jurist remarked, under that court's case law, "virtually anything is patentable." *Hughes Aircraft Co. v. United States*, 148 F.3d 1385, 1385 (Fed. Cir. 1998) (Clevenger, J., dissenting from denial of rehearing) (*citing State Street*, 149 F.3d 1368).

Despite the significance of the issues surrounding subject matter eligibility under section 101, particularly for business methods, IBM believes that the facts of this case do not present a suitable opportunity for analyzing and articulating the proper scope of subject matter for patent eligibility. The

present matter before the Court involves a medical diagnostic procedure, rather than an inchoate business method or other abstract technique. Moreover, the parties did not squarely address the section 101 issue below and the resulting record is thus not sufficiently developed with respect to the statutory subject matter inquiry. IBM therefore respectfully suggests that the Court not speak broadly to the issue of patentable subject matter, but rather await a more appropriate case to address this issue. Should, however, the Court decide to address the scope of subject matter eligibility for business methods, IBM wishes to provide its view on section 101 for the Court's consideration.

As a general matter, a robust notion of patentable subject matter best serves the United States in the twenty-first century. Within our innovation-driven economy, diverse industries have contributed numerous technical advances that are unquestionably suitable for patenting. The USPTO has, for example, appropriately awarded patents in the pharmaceutical, biotechnology, computer/electronics, biomedical, financial, mechanical and other important fields.

Unfortunately, decisions of the Federal Circuit (like *State Street*) have unduly expanded the scope of patent-eligible subject matter for business methods. This broad scope stands at odds with the Constitution and this Court's consistent statements that an invention must contribute to the "Progress of [the] . . . useful Arts" in order to be eligible for patenting. In that constitutional context, patentable advances must be tied to a particular machine or apparatus, or alternatively, must reside in the physical transformation of an article to a "different state or thing." *See Gottschalk v. Benson*, 409 U.S. 63, 70-71 (1972). The *State Street* standard overlooks this Court's precedent and fails to apply an important constraint upon the patent system without any doctrinal justification or alternative tempering principle.

In the absence of a compelling rationale to alter the understanding of "useful arts," IBM believes that this Court should reaffirm its existing standard for subject matter patentability which is restricted to inventions that involve technological contributions — namely, tangible products or processes that either (i) are tied to a particular machine or apparatus or (ii) cause transformation or reduction of an article to a different state or thing, and in either instance produce technologically beneficial results. IBM recognizes that the Court has previously used language suggesting that this standard may not be a rigid rule, but rather more akin to a presumption. In the intervening years, however, no situation has been presented to this Court which warrants any exception to this rule. This test sets forth a reasonable and balanced standard for subject matter eligibility.

The long-standing principles governing subject matter eligible for patenting should be maintained such that, for example, a method of painting a surface using the posterior of an infant (U.S. Pat. No. 6,213,778) and a method for making jury selection determinations (U.S. Pat. No. 6,607,389) are not patentable subject matter because they do not produce technologically beneficial results. IBM recognizes that some of its own business method patents may include claims that might not satisfy this standard.

The Federal Circuit accomplished its shift in patent policy without any evidence suggesting that incentives for innovation are currently needed with respect to abstract business methods and other non-technological innovations, and without due consideration of the impact that such a shift would have on the economy. Although no persuasive justification prompted the abrupt allowance — indeed explosion — of patents for abstract business methods, the breadth of coverage of such patents has raised significant concerns within the innovation community. Among them is concern that such patents, because they are not restricted to

a specific technological contribution, may effectively appropriate all conceivable solutions to a particular problem. Such an overbroad monopoly thwarts progress of the useful arts by precluding legitimate attempts to design around a patent and by providing unjustified rewards beyond the contribution of the inventor. As a result, should this Court speak to the issue of statutory subject matter beyond the facts of this case, IBM respectfully suggests that the Court should reaffirm, consistent with its precedent on section 101, that a technological contribution is required for subject matter patentability, thereby denying patents on abstract or non-technological business methods.

I. DIVERSE INDUSTRIES HAVE MADE TECHNICAL CONTRIBUTIONS THAT APPROPRIATELY FALL WITHIN THE SCOPE OF PATENTABLE SUBJECT MATTER

Throughout our history, the constitutional and statutory standard for patent-eligible subject matter has been sufficiently flexible to adapt to new technological innovations. For example, during the Industrial Revolution, the Court in *Cochrane v. Deener*, 94 U.S. 780, 781, 791 (1877), held that an improved method for manufacturing flour was patentable. More recently, in *Diamond v. Chakrabarty*, 447 U.S. 303, 318 (1980), the Court held that a new life form, a microbe capable of digesting petrochemicals, was patentable. At the dawn of the Information Age, the Court held that a claim directed to a chemical process which included a programmed digital computer was patentable. *Diehr*, 450 U.S. at 191-93. The USPTO has heeded the Court's direction, allowing patents on, *inter alia*, new pharmaceutical, biotechnology and financial services inventions.[3] IBM fully supports a robust scope of patentable subject matter for these

[3] *See, e.g.*, U.S. Patent Nos. 6,969,531 ("Sodium Hyaluronate Microsphere), 6,967,096 ("Thermostable Peptisade") and 6,606,606 ("Systems and Methods for Performing Integrated Financial Transaction").

and other important innovations which are rooted in technological contributions. Further, IBM recognizes that the patent system's ability to adapt to new technologies is consistent with the constitutional requirement of promoting the useful arts and, in particular, that a measured evolution of the scope of patentable subject matter is an important incentive for pioneering innovations.

Turning to the recent burst of business method patents and the significance of the issues surrounding subject matter eligibility of business methods, IBM believes that the facts of this case do not present a suitable predicate for broadly analyzing and articulating the proper scope of subject matter patentability under section 101. First, while IBM expresses no view on the merits of this case, the present matter before the Court involves a medical diagnostic procedure,[4] rather than an inchoate business method or other abstract technique. Second, the petitioner failed to preserve the issue of patentable subject matter in the lower courts or develop a complete record for its review. The petitioner did not, either at trial or on appeal, challenge the validity of the patent as being directed to non-statutory subject matter.[5]

While the question on which certiorari was granted is narrower than that posed to the Government,[6] IBM submits

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[4] The patent is directed to methods for assaying samples of body tissues to determine total homocysteine levels and methods for diagnosing vitamin B deficiency based on the elevated homocysteine levels. U.S. Patent No. 4,940,658, col. 3, ll. 6-62.

[5] *See* Brief for the United States as Amicus Curiae at 9-12, *Metabolite Labs., Inc. v. Lab. Corp. of Am.*, 370 F.3d 1354 (Fed. Cir. 2004), *cert. granted*, 126 S. Ct. 601 (U.S. Nov. 2, 2005) (No. 04-607).

[6] When the petition for certiorari was pending, this Court asked for the Government's views on the following question: "Is the patent invalid because one cannot patent 'laws of nature, natural phenomena, and abstract ideas'? *Diamond v. Diehr*, 450 U.S. 175, 185 (1981)." *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 125 Sup. Ct. 1413 (2005).

this brief to address the subject of patent eligibility under section 101, particularly for business methods, in the event the Court decides to undertake a broad review of subject matter patentability.

II. THE SCOPE OF PATENTABLE SUBJECT MATTER HAS BEEN EXPANDED BEYOND THE LIMITS ESTABLISHED BY THE CONSTITUTION AND THIS COURT'S PRECEDENT

A. The Constitution And This Court's Precedent Establish Limits Upon The Subject Matter Eligible For Patenting

Article I, Section 8 of the Constitution provides:

> The Congress shall have Power ... To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.

U.S. CONST. art. I, § 8, cl. 8. *See* THE FEDERALIST No. XLIII, at 294 (James Madison) (M. Walter Dunne 1901) ("The right to useful inventions . . . belong to the inventors."). Historical context confirms that the Constitution restricts the scope of patent eligible subject matter. For example, the English Statute of Monopolies of 1623, upon which the United States patent system is largely based, provided an exception to the general prohibition against monopolies by granting a "privilege for the term of fourteen years or under [for] the sole working or making any manner of new manufactures . . . to the . . . inventor . . . ." Statute of Monopolies, 1623, 21 Jac. 1, c.3 (Eng.), *reprinted in* 9 DONALD S. CHISUM, CHISUM ON PATENTS, App. 8-3 (2005). Notably, that Statute eliminated

commercial practices from the scope of patentable exclusivity:

> [T]hose who formulated the Constitution were familiar with the long struggle over monopolies so prominent in English history, where exclusive rights to engage even in *ordinary business activities* were granted so frequently by the Crown for the financial benefits accruing to the Crown only. It was desired that in this country any Government grant of a monopoly for even a limited time should be *limited to those things which serve in the promotion of science and the useful arts.*

In re Yuan, 188 F.2d 377, 380 (C.C.P.A. 1951) (emphasis added). Contemporaneous use of the term "useful art" by the Founding Fathers further confirms that patent-eligible subject matter is limited to technological or industrial innovations. The term "useful arts" was used in the context of the production of goods and the industrial, mechanical and manual arts, days before the Constitutional Convention of 1787 by a delegate to that Convention.[7] Likewise,

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[7] "Under all the disadvantages which have attended manufactures and *the useful arts*, it must afford the most comfortable reflection to every patriotic mind to observe their progress in the United States and particularly in Pennsylvania. . . . Permit me however to mention them under their general heads: meal of all kinds, ships and boats, malt and distilled liquors, potash, gunpowder, cordage, loaf-sugar, pasteboard, cards and paper of every kind, books in various languages, snuff, tobacco, starch, cannon, musquets, anchors, nails, and very many other articles of iron, bricks, tiles, potters ware, mill-stones, and other stone work, cabinet work, trunks and Windsor chairs, carriages and harness of all kinds . . . ." Tench Coxe, Delegate to the 1787 Constitutional Convention from Pennsylvania, An Address to an Assembly of the Friends of American

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Alexander Hamilton praised the patent system as a way of encouraging manufacturing industries and "[inventions] which relate to machinery" in the United States. ALEXANDER HAMILTON, THE REPORTS OF ALEXANDER HAMILTON: REPORT ON MANUFACTURES (Dec. 5, 1791) 115-16, 175-76 (Jacob E. Cooke ed., Harper & Row 1964).

Consistent with the constitutional foundation, the current patent statute, 35 U.S.C. § 101, provides:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

This Court has long held that the first three categories enumerated in section 101 — machines, manufactures and compositions of matter — refer to physical products. The Court has defined the term "machine" in section 101 to mean "a concrete thing, consisting of parts, or of certain devices and combination of devices." *Burr v. Duryee*, 68 U.S. (1 Wall.) 531, 570 (1864). "'Manufacture'" in section 101 means "'the production of articles for use from raw or prepared materials by giving to these materials new forms,

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Manufactures: Convened for the Purpose of Establishing a Society for the Encouragement of Manufactures and the Useful Arts, Read in the University of Pennsylvania, on Thursday the 9th of August 1787, 17-18 (R. Aitkin & Son 1787) (emphasis added); *see also* Joseph Barnes, *Treatise on the Justice, Policy, and Utility of Establishing an Effectual System for Promoting the Progress of Useful Arts* 4 (Francis Bailey 1792) (Patentable invention "consists in discoveries in science, and in the useful arts; by means of which agriculture, navigation, manufactures, and manual labor are, not only facilitated, but much promoted; and, indeed, to these they owe their present state of perfection.").

qualities, properties, or combinations, whether by hand-labor or by machinery.'" *Chakrabarty*, 447 U.S. at 308. "[C]omposition of matter" has been defined as "all compositions of two or more substances and . . . all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids." *Id.*

The fourth section 101 category — "process" — is defined in the patent statute as:

> process, art or method, and includes a new use of a known process, machine, manufacture, composition of matter, or material.

35 U.S.C. § 100(b). Although the meaning of the terms "process, art or method" is broad on its face, this Court's precedent "forecloses a purely literal reading of § 101." *Parker v. Flook*, 437 U.S. 584, 589 (1978); *see also Diehr*, 450 U.S. at 183 ("A process is a mode of treatment of certain materials to produce a given result. It is an act, or a series of acts, performed upon the subject-matter to be transformed and reduced to a different state or thing."). In particular, this Court has consistently distinguished between concrete, specific and technologically-grounded aspects of innovative contributions, which are protectable via the patent system, from underlying abstract or general principles, which are not.

In an early landmark decision regarding patentable subject matter, *O'Reilly v. Morse*, 56 U.S. (15 How.) 62, 113 (1854), the Court revoked Morse's eighth claim, which recited:

> *I do not* propose to *limit myself to* the *specific machinery* or parts of machinery described in the foregoing specification and claims; *the essence*

> *of my invention being the use of* the motive power of the electric or galvanic current, which I call *electro-magnetism, however developed for marking or printing intelligible characters, signs, or letters, at any distances*, being a new application of that power of which I claim to be the first inventor or discoverer.

Id. at 112 (emphasis added). The Court reasoned that the claim was "not warranted by law" because it would protect, and thereby prevent use of, all conceivable solutions to accomplish the recited result. *Id.* at 113.

> *If this claim can be maintained, it matters not by what process or machinery the result is accomplished.* For aught that we now know some future inventor, in the onward march of science, may discover a mode of writing or printing at a distance by means of the electric or galvanic current, without using any part of the process or combination set forth in the plaintiff's specification. . . . But yet if it is covered by this patent the inventor could not use it, nor the public have the benefit of it without the permission of this patentee.

Id. at 112-13 (emphasis added). The Court explained that Morse was only entitled to a patent for the method of using electro-magnetism to print marks or signs at a distance that he actually invented: "he has not discovered that the electro-magnetic current, used as a motive power, *in any other method, and with any other combination*, will do as well." *Id.* at 117 (emphasis added).

Twenty years later, in *Rubber-Tip Pencil Co. v. Howard*, 87 U.S. (20 Wall.) 498, 507 (1874), the Court invalidated a

claim reciting a rubber eraser having a hole to accept a pencil, explaining "an idea of itself is not patentable, but a new device by which it may be made practically useful is."

O'Reilly and *Rubber-Tip Pencil* are bedrock cases for determining the patent eligibility of subject matter. In the first instance, both cases confirm that the patent system does not protect all types of processes nor does it protect abstract ideas. These cases also reinforce the important policy goal of maintaining "basic tools of scientific and technological work" within the public domain. *See Gottschalk*, 409 U.S. at 67. *O'Reilly* in particular makes clear that process patents should not be allowed to appropriate all solutions to a problem. This Court has consistently applied the fundamental principles announced in *O'Reilly* and *Rubber-Tip Pencil* in the intervening years.

Notably, in a trilogy of cases decided at the dawn of the Information Age, the Court considered computer-related inventions and confirmed its early precedent as applied to new fields of endeavor. In *Gottschalk v. Benson*, 409 U.S. at 64, the patent claimed a "method for converting binary-coded decimal (BCD) numerals into pure binary numerals." "The claims were not limited to any particular art or technology, to any particular apparatus or machinery, or to any particular end use." *Id.* The claims "purported to cover any use of the claimed method in a general-purpose digital computer of any type." *Id.*

The question presented to the Court in *Gottschalk* was "whether the method described and claimed was a 'process' within the meaning of the Patent Act." *Id.* After reviewing a number of early decisions, the Court held that the claimed method was not patentable. *Id.* at 71-73. Much as "one may not patent an idea," one may not patent the "formula for converting BCD numerals to pure binary numerals." *Id.* at

71. "[T]he mathematical formula involved here has no substantial practical application except in connection with a digital computer, which means that if the judgment below is affirmed, the patent would wholly pre-empt the mathematical formula and in practical effect would be a patent on the algorithm itself." *Id.* at 71-72.

In reaching its decision, the Court acknowledged that the "[t]ransformation and reduction of an article 'to a different state or thing' is the clue to the patentability of a process claim that does not include particular machines." *Id.* at 70. *See, e.g., Expanded Metal Co. v. Bradford*, 214 U.S. 366, 385-86 (1909) (sustaining a patent on a process for expanding metal that involved mechanical operations).

Parker v. Flook, 437 U.S. at 585 involved claims drawn to a method for computing an "alarm limit" on any process variable involved in the catalytic chemical conversion of hydrocarbons. When a process variable, such as temperature, pressure, or flow rate, exceeded a predetermined "alarm limit," an alarm signaled "an abnormal condition indicating either inefficiency or perhaps danger." *Id.* The only difference between the claimed method and the previous conventional methods was the mathematical algorithm or formula used to calculate the alarm limit. *See id.* at 585-86.

The Court held that the claim was ineligible for patenting because it simply provided a formula for computing an updated alarm limit. *Id.* at 594-96. The application did not explain how to "select the appropriate margin of safety, the weighing factor, or any other variables, . . . [n]or [did] it . . . contain any disclosure relating to the chemical processes at work, the monitoring of process variables, or the means of setting off an alarm or adjusting an alarm system." *Id.* at 586.

Following the *Gottschalk* decision, the Court in *Parker* confirmed that a process does not automatically fall within the patentable subject matter of section 101 merely because a process implements a principle or mathematical formula in some specific fashion. *See Parker*, 437 U.S. at 593. To permit otherwise "would make the determination of patentable subject matter depend simply on the draftsman's art and would ill serve the principles underlying the prohibition against patents for 'ideas' or phenomena of nature." *Id.* "The rule that the discovery of a law of nature cannot be patented rests, not on the notion that natural phenomena are not processes, but rather on the more fundamental understanding that they are not the kind of 'discoveries' that the statute was enacted to protect." *Id.* An inventive application of a mathematical formula, principle or phenomenon of nature may be patented, but patentability cannot be supported "unless there is some other inventive concept in its application." *Id.* at 594.

Furthermore, the Court stated that "post-solution activity" — the adjustment of the alarm limit to the figure computed according to the formula — cannot "transform an unpatentable principle into a patentable process." *Id.* at 590. "A competent draftsman could attach some form of post-solution activity to almost any mathematical formula . . . [however, the] concept of patentable subject matter under § 101 is not 'like a nose of wax which may be turned and twisted in any direction . . . .'" *Id.* (*quoting White v. Dunbar*, 119 U.S. 47, 51 (1886)).

In *Diamond v. Diehr*, 450 U.S. at 177, the invention was "a process for molding raw, uncured synthetic rubber into cured precision products." According to the patent, the industry had been unable "to obtain uniformly accurate cures because the temperature of the molding press could not be precisely measured, thus making it difficult to . . . determine

cure time." *Id.* at 178. To overcome this problem, the method required, *inter alia*, constantly measuring the actual temperature inside the mold and then automatically feeding the temperature measurements into a computer which would repeatedly recalculate the cure time by use of a well-known equation. *See id.*

This Court held the claims to be patentable because "a physical and chemical process for molding precision synthetic rubber products falls within the § 101 categories of possibly patentable subject matter." *Id.* at 184. Here, the "claims were not directed to a mathematical algorithm or an improved method of calculation but rather recited an improved process for molding rubber articles by solving a practical problem which had arisen in the molding of rubber products." *Id.* at 181. "[T]he transformation of an article, in this case raw, uncured synthetic rubber, into a different state or thing cannot be disputed." *Id.* at 184. In fact, "[i]ndustrial processes such as this are the types which have historically been eligible to receive the protection of our patent laws." *Id.*

The Court further stated, "[a] claim drawn to subject matter otherwise statutory does not become nonstatutory simply because it uses a mathematical formula, computer program, or digital computer." *Id.* at 187. Rather, "when a claim containing a mathematical formula implements or applies that formula in a structure or process which, when considered as a whole, is performing a function which the patent laws were designed to protect (*e.g.*, transforming or reducing an article to a different state or thing), then the claim satisfies the requirements of § 101." *Id.* at 192.

On the other hand, "laws of nature, natural phenomena, and abstract ideas" are excluded from patent protection. *Id.* at 185. Scientific truths, or the mathematical expression

of them, are similarly outside the patent system, but "'a novel and useful structure created with the aid of knowledge of scientific truth may be [patentable].'" *Id.* at 188 (*quoting Mackay Radio & Telegraph Co. v. Radio Corp of Am.*, 306 U.S. 86, 94 (1939)).

In these and other relevant patent cases, the Court has developed several cogent principles that constrain subject matter patentability:

- "Excluded from . . . patent protection are laws of nature, natural phenomena, and abstract ideas." *Diehr*, 450 U.S. at 185.

- "A principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented, as no one can claim in either of them an exclusive right." *Le Roy v. Tatham*, 55 U.S. (14 How.) 156, 175 (1853).

- One may not patent an idea. *Gottschalk*, 409 U.S. at 71 (*citing Rubber-Tip Pencil*, 87 U.S. at 507).

- "Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." *Gottschalk*, 409 U.S. at 67.

- Mathematical algorithms are not patentable. *See Diehr*, 450 U.S. at 186; *Parker*, 437 U.S. at 586; *Gottschalk*, 450 U.S. at 71-72.

- One cannot patent all solutions to a problem. *See O'Reilly*, 56 U.S. at 113.

- "'It is for the discovery or invention of some practical method or means of producing a beneficial result or effect, that a patent is granted, and not for the result or effect itself.'" *Diehr*, 450 U.S. at 182 n.7 (*quoting Corning v. Burden*, 55 U.S. (15 How.) 252, 267-68 (1854)).

- Insignificant post-solution activity or limiting an abstract idea to one technological environment will not render an abstract idea patentable. *See Diehr*, 450 U.S. at 191-92; *Parker*, 427 U.S. at 590.

- "A claim covers and secures a process, a machine, a manufacture, a composition of matter, or a design, but *never the function or result* of either, nor the scientific explanation of their operation." *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 373 (1996) (emphasis added).

B. The Gravamen Of This Court's Precedent Is That Subject Matter Patentability Is Restricted To Inventions That Involve Technological Contributions

IBM believes a comprehensive understanding of subject matter patentability can be deduced directly from this Court's precedent. More specifically, patentable subject matter is restricted to inventions that involve technological contributions — namely, tangible products or processes that either (i) are tied to a particular machine or apparatus or (ii) cause transformation or reduction of an article to a different state or thing, and in either instance produce technologically beneficial results. In summarizing this Court's existing standard, IBM recognizes that the Court has used language suggesting that it may not be a definitive rule,

but rather more akin to a presumption.[8] In the intervening years, however, no situation has been presented to this Court to justify an exception to this Court's standard. This test sets forth a reasonable and balanced standard for subject matter eligibility.

The requirement for technological contribution is also consistent with numerous cases of this Court, referring to patents as properly directed toward "technology" and "technological growth and industrial innovation." *See, e.g., Gottschalk*, 409 U.S. at 64 ("The claims were not limited to any particular art or *technology*, to any particular apparatus or machinery, or to any particular end use.") (emphasis added); *Diehr*, 450 U.S. at 184 ("*Industrial processes* . . . have historically been eligible to receive the protection of our patent laws.") (emphasis added); *Pfaff v. Wells*, 525 U.S. 55, 63 (1998) ("the patent system represents a carefully crafted bargain that encourages both the creation and the public disclosure of new and useful advances in *technology*, in return for an exclusive monopoly for a limited period of time.") (emphasis added); *Bonito Boats v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 150-51 (1989) (same); *Markman*, 517 U.S. at 390 ("Congress created the Court of Appeals for the Federal Circuit as an exclusive appellate court for patent cases, H.R. Rep. No. 97-312, pp. 20-23 (1981), observing that increased uniformity would 'strengthen the United States patent system in such a way as to foster *technological growth and industrial innovation*.'") (emphasis added). IBM has been unable to find any cases from this Court that are inconsistent with the technological contribution requirement.

[8] The *Gottschalk* Court stated: "It is argued that a process patent *must* either be tied to a particular machine or apparatus or *must* operate to change articles or materials to a 'different state or thing.' We do not hold that no process could ever qualify if it did not meet the requirements of our prior precedents." *Gottschalk*, 409 U.S. at 71 (emphasis added). However, the Court has not undertaken to define circumstances where a process outside its precedent would qualify for patent protection.

Until recent years, lower courts had also recognized that patenting was confined to the "technological arts," a modern term recognized as synonymous with the phrase "useful arts" as it appears in the Constitution. *In re Waldbaum*, 457 F.2d 997, 1003 (C.C.P.A. 1972); *In re Bergy*, 596 F.2d 952, 959 (C.C.P.A. 1979) ("We have previously pointed out that the present day equivalent of the term 'useful arts' employed by the Founding Fathers is '*technological arts.*'") (emphasis added), *aff'd sub nom, Diamond v. Chakrabarty*, 447 U.S. 303 (1980); *In re Musgrave*, 431 F.2d 882, 893 (C.C.P.A. 1970) ("All that is necessary, in our view, to make a sequence of operational steps a statutory 'process' within 35 U.S.C. § 101 is that it be in the *technological arts* so as to be in consonance with the Constitutional purpose to promote the progress of 'useful arts.'") (emphasis added).

This test is rooted in the constitutional requirement that patents are granted to promote the progress of useful arts. In historical context, the useful arts required a technological contribution. This Court's precedent reinforces the need for a technological contribution for patent eligibility. A fair reading of this Court's precedent in the aggregate provides the foundation for the standard that a claim to a process or method is not patentable unless it either (i) is tied to a particular machine or apparatus or (ii) causes transformation or reduction of an article to a different state or thing, and in either instance produces technologically beneficial results.

C. The Decisions Of The Federal Circuit Have Applied An Unjustifiably Expansive Standard For Patent Eligibility Of Business Methods

A specific, and particularly troubling, arena where Federal Circuit rulings diverge from this Court's precedent is the eligibility of business methods for patenting. IBM is concerned over patenting methods of doing business lacking a technical contribution.[9]

Historically, methods of doing business were not patentable subject matter,[10] and the 1952 Patent Act did not

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[9] Examples of abstract business methods include U.S. Patent Nos. 5,947,526 (claim 1 reciting method for tracking personal expenditures) and 5,668,736 (claim 1 reciting method for remodeling an existing building).

[10] *See, e.g., Hotel Security Checking Co. v. Lorraine Co.*, 160 F. 467, 469-72 (2d Cir. 1908) ("cash-registering and account-checking" unpatentable "system of transacting business disconnected from the means for carrying out the system . . . ."); *Ex Parte Turner*, 1894 Dec. Comm'r Pat. 36, 36-37 (method to secure reading of advertisements not patentable because, *inter alia*, process carried no physical effect; "a plan or theory of action which, if carried into practice, could produce no physical results proceeding direct from the operation of the theory or plan itself is not an art within the meaning of the patent laws."); *Ex Parte Abraham*, 1869 Dec. Comm'r Pat. 59 (method for detecting and preventing tax evasion by employing stamps to be severed upon attachment to an article unpatentable; "[i]t is contrary . . . to the spirit of the law . . . to grant patents for methods of book-keeping . . . ."); *Loew's Drive-in Theatres, Inc. v. Park-In Theatres, Inc.*, 174 F.2d 547, 553 (1st Cir. 1949) (patent claiming arranging automobiles such that occupants would have an unobstructed view of a screen or stage did "not involve an exercise of the faculty of invention"); *Seagram & Sons, Inc. v. Marzall*, 180 F.2d 26, 27-28 (D.C. Cir. 1950) (method for testing beverages and like products to make advance determination of

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change this principle. "Although the term 'process' was not added to 35 U.S.C. § 101 until 1952, a process [as shaped by this Court's precedent] has historically enjoyed patent protection because it was considered a form of 'art' as that term was used in the 1793 Act." *Diehr*, 450 U.S. at 182 (*citing Corning*, 56 U.S. (How. 15) at 267-68). In an oft-quoted comment, Judge Rich explained that:

> Section 101, entitled "Inventions patentable," enumerates the categories of inventions subject to patenting. Of course, not every kind of an invention can be patented. Invaluable though it may be to individuals, the public, and national defense, the invention of a more effective organization of the materials in, and the techniques of teaching a course in physics, chemistry, or Russian is not a patentable invention because it is outside of the enumerated [statutory] categories.... Also outside that group is one of the greatest inventions of our times, the diaper service.

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consumer reactions and preferences not "new and useful art, machine, manufacture, or any new and useful improvements thereof"); *In re Patton*, 127 F.2d 324, 327-28 (C.C.P.A. 1942) (system of fighting fires using standardized and interchangeable fire fighting equipment not patentable subject matter; "a system of transacting business, apart from the means for carrying out such system, is not within . . . [the patent statute] . . . nor is an abstract idea or theory, regardless of its importance or the ingenuity with which it was conceived, apart from the means for carrying such idea or theory into effect, patentable subject matter."); *In re Wait*, 73 F.2d 982, 982-83 (C.C.P.A. 1934) (method of buying and selling stocks, wherein one party advertised offer, another party accepted offer and such transaction was recorded, constituted unpatentable method of doing business); *In re Sterling*, 70 F.2d 910, 911-12 (C.C.P.A. 1934) (patent application directed to a particular arrangement of printed matter on bank checks and stubs not patentable subject matter).

Giles S. Rich, *Principles of Patentability*, 28 GEO. WASH. UNIV. L. REV. 393, 393-94 (1960).[11]

The dicta in the Federal Circuit decision in *State Street*, however, created a dramatic sea-change in the patentability of inchoate business methods. *State Street* involved a patent generally directed to a data processing system for implementing an investment structure which was developed for use in Signature's business as an administrator and accounting agent for mutual funds. 149 F.3d at 1370.

The district court invalidated the patent for failure to claim statutory subject matter under section 101. *Id.* The Federal Circuit reversed the district court, ruling that the claims were directed to patentable subject matter because they produced a "useful, concrete and tangible result." *Id.* at 1375.

> [T]he transformation of data, representing discrete dollar amounts, by a machine through a series of mathematical calculations into a final share price, constitutes a practical application of a mathematical algorithm, formula, or calculation, because it produces "a useful, concrete and tangible result" — a final share price momentarily fixed for recording and reporting purposes and even accepted and relied upon by regulatory authorities and in subsequent trades.

Id. at 1373.

While the Federal Circuit's holding in *State Street* regarding the claim at issue can be justified, IBM believes

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[11] Judge Rich was one of the principle drafters of the 1952 Patent Act as well as a Judge of the Court of Customs and Patent Appeals and the Court of Appeals for the Federal Circuit from 1957 to 1999.

that dicta in the decision ignited the explosion of non-technological business method patents seen today. The Federal Circuit concluded that the claim was drawn to a system, not a method of doing business, and it included a number of structural elements as limitations — thus, the claimed invention was a machine that implemented a process. However, the expansive dicta in *State Street* are inconsistent with this Court's precedent. *See, e.g., id.* at 1375 ("We take this opportunity to lay this ill-conceived exception [i.e., that business methods are not patentable] to rest.").

In the context of business methods, the broad dicta in *State Street* have reduced the historically separate subject matter requirement of section 101 to a mere "practical utility" determination. *State Street*, 149 F.3d at 1375 ("The question of whether a claim encompasses *statutory subject matter should* not *focus on* which of the four categories of subject matter a claim is directed to — process, machine, manufacture, or composition of matter — but rather on the essential characteristics of the subject matter, in particular, its *practical utility*.") (emphasis added).

The contrast in approach is clearly evident from this Court's precedent. In *Parker v. Flook*, for example, the case turned "entirely on the proper construction of § 101 of the Patent Act, which describes the subject matter that is eligible for patent protection." 437 U.S. at 588. Whether subject matter is eligible for patenting is an entirely separate inquiry from whether the claimed invention provides some useful result, i.e., whether it meets the separate utility requirement of section 101. *See id.*

No decision of this Court supports the broad proposition that merely because a method yields a useful result it should *ipso facto* be eligible for patenting, as is the current standard applied by the Federal Circuit. Rather, this Court has

recognized that the utility requirement of 35 U.S.C. § 101 is a distinct and separate test from the eligibility requirement of section 101. A mere "useful result" standard is much too lenient to determine whether subject matter is eligible for patenting. As Judge Rich so aptly stated decades ago, the diaper service (prior to the advent of disposable diapers) was undoubtedly one of the greatest business creations in its day, invaluable to countless individuals. However, despite its usefulness, the diaper service does not fall within one of the four enumerated categories of section 101. *See* Giles S. Rich, *Principles of Patentability*, 28 GEO. WASH. UNIV. L. REV. 393, 39394 (1960).

The standard espoused in *State Street* merely addresses the usefulness of the outcome. *See State Street*, 149 F.3d at 1375. This standard is at odds with the principles of patentability established by the Constitution and this Court and the ambit of patentable subject matter as established in the 1952 Patent Act. Ignoring the enumerated categories of statutory subject matter as a threshold inquiry of patentability makes the categories mere drafting protocols. *See Parker*, 437 U.S. at 590 (cautioning that a competent draftsmen could attach some post-solution activity to "transform an unpatentable principle into a patentable process" within section 101).

Although *State Street* purported to quote from *Diehr* that "anything under the sun made by man is patentable," that quote was taken out of context. *State Street*, 149 F.3d at 1373. Congressional reports employed that phrase only with respect to machines and manufactures. *See* S. REP. No. 82-1979, at 2399 (1952) ("A person may have 'invented' a machine or a manufacture, which may include anything under the sun that is made by man, but it is not necessarily patentable under section 101 unless the conditions of the title are fulfilled."); H. R. REP. No. 82-1923 (1952) (same). Certainly, section 101 does not say "anything under the sun made by man" is patentable subject matter, but rather references four specific categories.

Acquiescing to the demands of patent applicants and the *State Street* dicta, the USPTO has now dramatically changed course as well. Thus, for example, the USPTO recently promulgated "interim guidelines" stating that an invention need not lie within the "technological arts" to be patented. *Official Gazette of the United States Patent and Trademark Office*, 1300 O.G. 142, No. 4 (Nov. 22, 2005).[12]

Issued patents from such diverse areas as architecture, athletics, insurance, painting, psychology, and the law itself, reveal just how far afield the patent system has gone in granting patents in virtually any area of human endeavor, such as teaching a golf putting stroke or a method for lifting a box.[13]

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[12] In reaction to the sweeping impact of *State Street*, Congress passed the First Inventor Defense Act of 1999, i.e., 35 U.S.C. § 273, to provide a defense to infringement of a business method patent if the accused infringer "had, acting in good faith, actually reduced the subject matter to practice at least 1 year before the effective filing date of such patent, and commercially used the subject matter before the effective filing date of such patent." First Inventor Defense Act of 1999, Pub. L. No. 106-113, 113 Stat. 1536 (codified as amended at 35 U.S.C. § 273 (2000)). Beyond that limited purpose, there is nothing in the legislative history to suggest Congress intended to make any other changes to the United States patent laws. Thus, this Court's precedent on section 101 patent eligibility for business methods — as articulated in the *Gottschalk-Parker-Diehr* trilogy — remains the controlling standard.

[13] *See, e.g.*, U.S. Patents Nos. 5,498,162 ("Method For Demonstrating a Lifting Technique"), 6,447,403 ("Method and Apparatus for Improving Putting Skill"), 6,912,510 ("Methods of Exchanging an Obligation"), 5,190,458 ("Character Assessment Method"), and 5,809,484 ("Method and Apparatus For Funding Education By Acquiring Shares of Students Future Earnings").

III. NO SOUND INNOVATION POLICY SUPPORTS PATENTS ON NON-TECHNOLOGICAL METHODS OF DOING BUSINESS

Not only is an unrestricted sense of patentable subject matter disfavored by sound innovation policy, it conflicts with the requirement, stipulated by the Constitution and consistently articulated by this Court's precedent, that patentable subject matter must fall within the "useful arts."

A. Patent-Based Incentives Are Not Needed To Spur Business Method Innovation

The decision to issue patents on particular subject matter involves, in the words of Thomas Jefferson, a determination of those "'things which are worth to the public the embarrassment of an exclusive patent . . . .'" *Graham v. John Deere Co.*, 383 U.S. 1, 9 (1966).

In this regard, the evidence suggesting a sudden need for patent-based incentives to promote the development of business concepts is conspicuous by its absence. "Nowhere in the substantial literature on innovation is there a statement that the United States economy suffers from a lack of innovation in methods of doing business. Compared with the business practices of comparable economies we seem to be innovators . . . ." Leo J. Raskind, *The State Street Bank Decision: The Bad Business of Unlimited Patent Protection for Methods of Doing Business*, 10 FORDHAM INTELL. PROP., MEDIA & ENT. L.J. 61, 92 (1999). Among the reasons for the persistent favorable record of commercial entrepreneurship in the United States are existing federal and state regimes, including unfair competition law, trade secrets, copyright, and the misappropriation doctrine, that have long policed free riding and allowed business pioneers to reap the rewards of their ideas. *See id.* at 93. In conjunction with market-based

incentives, including the desire to seize first-mover and learning-curve advantages, the current legal framework has resulted in a flourishing environment for business innovation in the United States. No plausible argument supports the view that protecting non-technological business methods through our patent system is needed to solve a market failure problem, fill a legal void, or ultimately enhance social welfare.

B. Business Method Patenting Raises Significant Competitive Concerns

Although no convincing justification exists for allowing patents on non-technological methods of doing business and other abstract ideas, the breadth of coverage of such patents has raised significant competitive concerns. Among them is that such patents are not restricted by the Constitution and the precedent articulated by this Court. Rather, they may effectively appropriate all possible solutions to a particular problem. This direct restraint upon the ability of competitors to develop alternatives to the patented invention thwarts a principal aspiration of the patent system, fostering new alternatives. *See Slimfold Mfg. Co. v. Kinkead Indus., Inc.*, 932 F.2d 1453, 1457 (Fed. Cir. 1991) ("Designing around patents is, in fact, one of the ways in which the patent system works to the advantage of the public in promoting progress in the useful arts, its constitutional purpose."); *Brenner v. Manson*, 383 U.S. 519, 534 (1966) ("Until [a] process claim has been reduced to production of a product shown to be useful, the metes and bounds of that monopoly are not capable of precise delineation. It may engross a vast, unknown, and perhaps unknowable area.").

Consider, for example, the ubiquitous automated teller machine ("ATM"). A review of the patent rolls reveals numerous ATM patents concerning such mechanical, electrical, and computer-implemented inventions as card

readers, touch screens, cash dispensers, statement printers, and antitheft mechanisms. As evidenced by the robust competition within the contemporary ATM industry, such patents have both preserved the incentives of industry participants to innovate, yet allowed their competitors to market alternative designs. However, in view of the Federal Circuit's endorsement of patents on inchoate business methods, a contemporary inventor's claim to the very concept of an ATM would be considered eligible for patenting under section 101. Much like claim 8 of Morse's telegraphy patent, such a patent would effectively prevent all others from designing alternative mechanisms for meeting the same marketplace needs. The potential adverse impact of this hypothetical patent upon competition not just in the ATM industry, but within the banking industry itself, is apparent.

The lack of a plausible justification for patents on abstract business methods and human behavior, coupled with the anticompetitive consequences of issuing these patents, counsels that this Court continue to restrict patentable subject matter to instantiated products and processes. Modern society's dizzying pace of technological change, with its accompanying changes to marketplace conditions and commercial practices, should by no means lead to an alteration of these established principles.

Nor does this Court's recognition that the patent system should keep apace with unforeseeable fields of scientific or technological discovery, *see Chakrabarty*, 447 U.S. at 315-16, compel a contrary result. Abstract business concepts are not an unforeseeable field, and, in fact, they long predate the patent system. *See, e.g.*, John R. Thomas, *The Patenting of the Liberal Professions*, 40 B.C. L. Rev. 1139, 1145-46 (1999). Moreover, by definition, abstract or inchoate business methods are not scientific or technological. *See* Malla Pollack, *The Multiple Unconstitutionality of Business Method*

Patents: Common Sense, Congressional Consideration, and Constitutional History, 28 RUTGERS COMP. & TECH. L.J. 61, 77-78 (2002).

In *State Street*, the Federal Circuit articulated broad-sweeping dicta without making an inquiry into whether the patenting of inchoate methods of doing business raises competitive concerns and whether traditional patent-based incentives were actually needed to spur methods of doing business. "Jefferson saw clearly the difficulty in 'drawing a line between the things which are worth to the public the embarrassment of an exclusive patent, and those which are not.'" *Graham*, 383 U.S. at 9. This Court should return the ambit of patentable subject matter to that range of innovation which truly justifies tolerating the "embarrassment of an exclusive patent."

CONCLUSION

Should the Court decide to address the issues of subject matter eligibility for business methods, for all the foregoing reasons, the Court should hold that patentable subject matter under section 101 is restricted to inventions that involve technological contributions — namely, tangible products or processes that either (i) are tied to a particular machine or apparatus or (ii) cause transformation or reduction of an article to a different state or thing, and in either instance produce technologically beneficial results.

Respectfully submitted,

DAVID J. KAPPOS
IBM CORPORATION
One North Castle Drive
Armonk, NY 10504
(914) 765-4343

PAIK SABER
IBM CORPORATION
650 Harry Road
San Jose, CA 95120
(408) 927-3390

CHRISTOPHER A. HUGHES
Counsel of Record
MORGAN & FINNEGAN, L.L.P.
3 World Financial Center
New York, NY 10281
(212) 415-8700

JOHN R. THOMAS
GEORGETOWN UNIVERSITY
LAW CENTER
600 New Jersey Avenue, NW
Washington, DC 20001
(202) 662-9000

Counsel for Amicus Curiae
International Business Machines Corporation

December 23, 2005

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IN THE

Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS, DBA LABCORP,

Petitioner,

v.

METABOLITE LABORATORIES, INC., ET AL.

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF PATIENTS NOT PATENTS, INC., AS AMICUS CURIAE IN SUPPORT OF PETITIONER

JEFFREY LIGHT
PATIENTS NOT PATENTS, INC.
1712 Eye St., NW Suite 915
Washington, DC 20006
(202)277-6213

EDWARD J. ELDER
Counsel of Record
Klimaski and Associates, PC
1819 L St., NW, Seventh Floor
Washington, DC 20036
(202)296-5600

December 23, 2005

WILSON-EPES PRINTING CO., INC. – (202) 789-0096 – WASHINGTON, D. C. 20001

QUESTION PRESENTED

Whether a method patent setting forth an indefinite, undescribed, and non-enabling step directing a party simply to "correlate[e]" results can validly claim a monopoly over a basic scientific relationship used in medical treatment such that any doctor necessarily infringes the patent merely by thinking about the relationship after looking at a test result.

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INTEREST OF AMICUS CURIAE[1]

Amicus curiae Patients not Patents (PNP)[2] is a nonprofit organization dedicated to ensuring access to healthcare through litigation, advocacy, and education. PNP is organized around the principle that medical treatment should not be denied or restricted because of the existence of patents or other intellectual property barriers. Over the past year, PNP has had success in challenging the validity of patents on drugs owned by pharmaceutical companies through administrative proceedings at the U.S Patent and Trademark Office. Additionally, PNP protects consumer interests by conducting litigation against makers of dietary supplements for false advertising—specifically falsely marking unpatented products as patented.

PNP has an interest in this case because the Court's decision will have a significant effect on intellectual property barriers to health care. PNP also has an interest in this case because it will affect PNP's success in administratively challenging patents before the USPTO.

SUMMARY OF ARGUMENT

The claim at the center of the controversy between LabCorp and Metabolite is directed to a mental process for recognizing that a natural phenomenon has occurred. Because neither mental processes nor natural phenomena are pat-

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[1] Letters of consent to the filing of this brief from all parties have been filed with the Clerk. This brief was not authored in whole or in part by counsel for a party. No person or entity other than amicus curiae, its members, or its counsel made a monetary contribution to preparation or submission of this brief.

[2] Patients not Patents, *at* http://www.patientsnotpatents.org.

entable subject matter, the claim is invalid. Upholding the claim would lead to a proliferation of patents for purely mental processes, which would in turn harm both individual patients as well as public health.

ARGUMENT

I. UPHOLDING THIS PATENT WILL OPEN THE FLOODGATES FOR PATENTS CONTAINING MENTAL STEPS

If this Court finds that Claim 13 is directed to patentable subject matter, this Court will broaden the scope of what may be patentable to cover subject matter that had been previously unpatentable. Since the Federal Circuit ruled against LabCorp in June of 2004, the United States Patent and Trademark Office has received an increasing number of applications drawn to what had been considered by many patent practitioners as nonstatutory subject matter.[3] Some of these mirror the structure of Claim 13:

"A method for determining the prognosis of a patient suffering from cancer . . . the method comprising . . . *correlating* the tubulin isotype level with an indication of unfavorable prognosis . . . or . . . favorable prognosis" (2005/0272824, Claim 1) (emphasis added). This claim language illustrates how applicants may try to claim a monopoly where the out-

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[3] *See, e.g.*, published patent applications: 2005/0260680, 2005/0260654, 2005/0255537, 2005/0255484, 2005/0244890, 2005/0214760, 2005/0191664, 2005/0095591, 2005/0130230, 2005/0130233, 2005/0262031, 2005/0260683, 2005/0250162, 2005/0171432, 2005/0142618, 2005/0130250, 2005/0130250, 2005/0106104, 2005/0095579, *available at* http://www.uspto.gov.

come of the correlation only speaks to a vague unfavorable or favorable result.

"A method of evaluating a risk of occurrence of a medical condition in a patient, the method comprising: *receiving a patient dataset* for the patient; and *evaluating the dataset with a model predictive of the medical condition*" (2005/0262031, Claim 1) (emphasis added). Here, the applicant even eliminates Claim 13's modest limitation, "assaying." Instead, the claim, as drafted, would encompass the receipt of data by any means. Thus, the claim language seeks protection not just for the interpretation of one test, or the diagnosis of one disease, but for a general strategy of practicing medicine.

"A method for detecting and diagnosing neural injury and/or neuronal disorders comprising: *detecting* at least one or more proteolytic enzyme biomakers. . . and; *correlating the detection* of one or more protein biomarkers with a diagnosis of neural injury and/or neuronal disorders, wherein the *correlation takes into account the detection* of one or more protein biomarkers in each diagnosis, *as compared to normal subjects*" (2005/0260697, Claim1) (emphasis added). Here, the claim is not specific to any defined relationship between test result and a disease.

Further, the decision to uphold the validity of this claim may have broader reach than is initially evident. To meet constitutional requirements, the Court of Customs and Patent Appeals, predecessor to the Federal Circuit, whose opinions are considered *en banc* authority within the Federal Circuit, limited statutory subject matter in a process patent to the technological arts. *In re Musgrave*, 431 F.2d 882, 893 (C.C.P.A. 1970). This Court has never explicitly adopted such a standard.[4] *Amicus* asks the Court to bear this addi-

[4] Justice Stevens mentioned the "technological arts" standard in his dissent in *Diamond v. Diehr*, 450 U.S. 175, 200 (1981).

tional factor in mind when considering whether to expand the scope of patentable subject matter.

II. INDIVIDUAL PATIENTS WILL BE HARMED BY UPHOLDING CLAIM 13

Upholding Claim 13 as valid will interfere with the doctor-patient relationship. Testing for homocysteine alone does not infringe the patent. But it does produce results that someone, such as a doctor, has to interpret for the data to be meaningful in a clinical context. Interpreting the results alone does not infringe the patent, but someone has to order the assay. A doctor who orders an assay and analyzes whether the natural phenomenon–the correlation between homocysteine and vitamin deficiency–occurred, may infringe Claim 13, as the lower courts' decisions indicate. *E.g., Metabolite Labs., Inc. v. Lab. Corp.*, No. 99-Z-870 (D. Colo. Dec. 3, 2001), *aff'd by Lab. Corp. v. Metabolite Labs., Inc.*, No. 03-1120 (Fed. Cir. Jun. 8, 2004). Thus, even if the doctor orders the test and receives the raw data, he or she may choose to provide the patient with the data, rather than interpret it, to avoid infringement liability.

Increasingly, patients are looking to Internet web pages for help in understanding their health status. Unfortunately, patients are likely to misinterpret the raw data to which they do have access. A proactive patient may, for example, discover a web page that discloses a relationship between total homocysteine levels and vitamin B12 or folic acid deficiency. However, the information on that web page may be incorrect, incomplete, or misunderstood by the patient. The patient's physician may be reluctant to discuss the matter with the patient for fear of creating evidence that he or she correlated the test results with a deficiency of vitamin B12 or folate, thereby infringing on the patent. Thus, Claim 13

harms patients by inhibiting honest communication with their physician.

Although 35 USC § 287(c) limits the liability of a medical practitioner performing a medical activity from patent infringement,[5] the statute would not apply to the claim in controversy. First, the patent in question is based on an application having an effective filing date before Sept. 30, 1996, and is therefore exempt under § 287(c)(4). Second, subsection 2(a) defines "medical activity" as "the performance of the medical or surgical procedure on the body." Because Claim 13 is not directed to a procedure to be performed on the body, the physician may be subject to suit by the patentee.

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[5] § 287(c) provides: (c) (1) With respect to a medical practitioner's performance of a medical activity that constitutes an infringement under section 271(a) or (b) of this title [35 USCS § 271(a) or (b)], the provisions of sections 281, 283, 284, and 285 of this title [35 USCS §§ 281, 283, 284, and 285] shall not apply against the medical practitioner or against a related health care entity with respect to such medical activity. (2) For the purposes of this subsection: (A) the term "medical activity" means the performance of a medical or surgical procedure on a body, but shall not include (i) the use of a patented machine, manufacture, or composition of matter in violation of such patent, (ii) the practice of a patented use of a composition of matter in violation of such patent, or (iii) the practice of a process in violation of a biotechnology patent. (B) the term "medical practitioner" means any natural person who is licensed by a State to provide the medical activity described in subsection (c)(1) or who is acting under the direction of such person in the performance of the medical activity. . . . (E) the term "body" shall mean a human body, organ or cadaver, or a nonhuman animal used in medical research or instruction directly relating to the treatment of humans. (4) This subsection shall not apply to any patent issued based on an application the earliest effective filing date of which is prior to September 30, 1996.

III. PUBLIC HEALTH RESEARCH AND INTERVENTIONS ARE HARMED BY PATENTS ON INTERPRETING MEDICAL TESTS

One of the strategies used by public health researchers to determine the cause of disease is an examination of the incidence and prevalence of the disease in different populations. G. Rose, *Sick Individuals and Sick Populations*, Int'l J. of Epidemiology 14, 32-38 (1985), *reprinted in* Gostin, *Public Health Law and Ethics: A Reader*, 58-66 (2002). In contrast, studies which seek to determine why a particular patient has become sick are generally considered individual-centered studies. It is apparent that the availability and cost of licenses for the method described in Claim 13 would impact a physician's determination as to whether a particular patient's symptoms are caused by a deficiency of either vitamin B12 or folate. However, the cost and availability of licenses for the patented method would also affect the ability of researchers to perform population-based studies.[6]

For example, studies of total homocysteine levels in members of different populations have revealed an increased prevalence of folate deficiency in African-American elderly women compared to white elderly women. Stabler, *Racial Differences in Prevalence of Cobalamin and Folate Deficiencies in Disabled Elderly Women. See also* T.G. DeLoughery, G.T. Gerhard, A. Evans, et al., *Elevated Homocyst(e)ine (Hcy) Levels in Premenopausal Black Women are Due to Nutritional and not Genetic Factors*. Blood 88, 471 (1996)(abstr). The prevalence of B12 and folate deficiency has also been studied in connection with income, education, sex, military service and other socioeconomic conditions. S.J.

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[6] Epidemiologists are not protected by 35 U.S.C. 287(c) because their analysis does not constitute a "medical activity."

Bradley, R.L. Sacco, J.K. Roberts, et al. *Race-Ethnicity and Other Environmental Determinants of Serum Homocysteine in Northern Manhattan*. Stroke 29, 277 (1998) (abstr).

The statistical analysis in each of these studies contributes to society's understanding of the disease. Should each of the multitudes of factors found to correspond with deficiency, however weak the connection, be nevertheless patentable? If so, each newly identified risk factor would inhibit, rather than enhance, research conducted through standard analytic tools such as multivariate regression models. On the other hand, it would be contrary to precedent for the determination of patentable of subject matter under 35 U.S.C. § 101 to depend on the strength of the correlation between two or more variables. "Either the subject matter falls within Section 101 or it does not." *Animal Legal Defense. Fund v. Quigg*, 932 F.2d 920, 930 (Fed. Cir. 1991).

CONCLUSION

The threat posed by patent applicants to individual patients and the public health and research is real. Amicus Curiae asks the Court to find Claim 13 invalid under 35 USC §101 as claiming unpatentable subject matter.

Respectfully submitted,

Jeffrey Light
Patients not Patents, Inc.
1712 Eye St., NW Suite 915
Washington, DC 20006
(202)277-6213

Edward J. Elder
Counsel of Record
Klimaski and Associates, PC
1819 L St., NW, Seventh Floor
Washington, DC 20036
(202)296-5600

Attorney for Amicus Curiae

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IN THE

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LABORATORY CORPORATION OF AMERICA HOLDINGS, DBA LABCORP, PETITIONER

v.

METABOLITE LABORATORIES, INC., ET AL., RESPONDENTS

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF AMICUS CURIAE PEOPLE'S MEDICAL SOCIETY IN SUPPORT OF PETITIONER

LORI B. ANDREWS
Counsel of Record
DEBRA GREENFIELD
CLEMENTS RIPLEY
Chicago-Kent College of Law
565 West Adams Street
Chicago, IL 60611
Tel: 312-906-5359

FRANCIS C. J. PIZZULLI
718 Wilshire Boulevard
Santa Monica, CA 90401
Tel: 310-451-8020

December 22, 2005

QUESTION PRESENTED

Whether a method patent setting forth an indefinite, undescribed, and non-enabling step directing a party simply to "correlat[e]" test results can validly claim a monopoly over a basic scientific relationship used in medical treatment such that any doctor necessarily infringes the patent merely by thinking about the relationship after looking at a test result.

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Albert A. Walker, *Text-Book of the Patent Laws of the United States of America* (L.K. Strouse & Co., 2d ed. 1889) 7

STATEMENT OF INTEREST OF AMICUS CURIAE PEOPLE'S MEDICAL SOCIETY[1]

Amicus Curiae People's Medical Society, an Internal Revenue Code Section 501(c)(3) non-profit organization, is the largest patients' advocacy group in the United States and is a recognized authority on health care issues. Its mission is to enhance the availability of health care information to consumers and to encourage the health care system to be more responsive to consumers. The People's Medical Society is regularly consulted by government agencies, health care institutions, and companies designing health care products and pharmaceuticals for insights into the patients' perspective. The Society has served in an advisory capacity to the Health Care Financing Administration of the Federal Department of Health and Human Services on Medicare issues, and its current president, Charles Inlander, is a member of the Medical Error and Drug Safety Committee of the National Academy of Sciences, Institute of Medicine. As President of the People's Medical Society, Mr. Inlander has also served as a health commentator for National Public Radio in over 250 broadcast segments.

Since its inception in 1983, the People's Medical Society has released over 100 books, as well as hundreds of articles, fact sheets, and newsletters pertaining to the diagnosis and treatment of medical conditions. Over 7,000,000 copies of its books have been sold; the value of the medical information in these books is attested to by the honors these books have been accorded.[2] These publications further the

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[1] Pursuant to S. Ct. R. 37.6, People's Medical Society states that neither petitioner's nor respondents' has authored any portion of this brief. No financial contribution was made for preparation of this brief by anyone other than *Amicus* and its counsel. By letters filed with the Clerk of the Court, the parties have consented to the filing of this brief.

[2] For example, Charles Inlander et al., *Medicine on Trial* (Prentice Hall, 1988) was honored as Book of the Year by the American Nursing Association's *American Nursing Journal*. Charles Inlander, *The Men's*

organization's pledge "to put previously unavailable information into the hands of ordinary people so that they can make informed decisions about their own health care" and to "publish information designed to make every American a smart health care consumer."[3]

The activities of the People's Medical Society are designed to benefit patients by enhancing medical care, medical information, and medical research. If claim 13 of U.S. Patent No. 4,940,658 (the '658 patent) is upheld, each of these important activities will suffer. Moreover, if claim 13 is upheld, the charitable purpose of the People's Medical Society itself will be thwarted. The People's Medical Society could be construed to have done precisely what the Federal Circuit held actionable in this case. In its book, *Vitamins & Minerals: Questions You Have... Answers You Need* (1993), the People's Medical Society disclosed that homocysteine levels were related to vitamin deficiency.[4]

The unique voice of the People's Medical Society is particularly relevant in a patent case. In the United States, unlike Europe, there is no general procedure for third parties representing consumers to voice concerns at the time the U.S. Patent and Trademark Office is considering issuing a patent. Generally, the only entities that can challenge patents in litigation are entities that are themselves infringing the

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Health and Wellness Encyclopedia (MacMillan Publishing Company, 1998) was honored as reference book of the year by the New York Public Library, and the same honor was given in a previous year to Charles Inlander et al., *The People's Medical Society Health Desk Reference* (Hyperion Books, 1996).

[3] People's Medical Society: About the Society, *available at* <http:peoplesmed.org/abutmenu.html>.

[4] Q: How can I be checked for a B_{12} deficiency?

A: Blood tests are used. Usually a serum B_{12} test is done first. If that's low, physicians test to check for two other blood components associated with B_{12} deficiency: homocysteine and methylmalonic acid. . . .

Ellen Moyer, *Vitamins & Minerals : Questions You Have.. Answers You Need* 104 (People's Medical Society, 1993).

patent. In many instances, both sides in patent lawsuits have incentives to argue in favor of patentability of broad types of inventions and discoveries, even when challenging a particular patent, because each side in the dispute has its own patent portfolio it wants to protect or can readily pass royalty charges on to the consumer.[5] In contrast, the People's Medical Society does not hold any patents and thus can raise fundamental legal and policy concerns.

The lack of a mechanism for a consumer voice in the process for granting a patent is particularly troublesome, given the fact that much medical research in the United States is funded by the public. Over $27,887,512,000 in taxpayer funds were given to the National Institutes of Health (NIH) for medical research in 2004.[6] In fact, according to the '658 patent, the inventors relied on government funding for their work that led to the '658 patent. In addition, inventors' medical articles note their use of federal funding. *See, e.g.*, S.P. Stabler et al., *Elevation of Total Homocysteine in the Serum of Patients with Cobalamin or Folate Deficiency Detected by Capillary Gas Chromatography – Mass Spectrometry*, 81 J. Clin. Invest. 2, 466, 473 (February 1988).

The Court's decision in this case will have a substantial impact on patients, including those whose interests the People's Medical Society champions. It will also have an impact on the services the non-profit People's Medical Society performs.

SUMMARY OF ARGUMENT

The U.S. Constitution, Article I, Section 8, Clause 8, gives Congress the power "to promote the progress of

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[5] Lori B. Andrews, *Genes and Patent Policy: Rethinking Intellectual Property Rights*, 3 Nature Reviews Genetics 805-806 (October 2002).

[6] National Institutes of Health, About NIH, *available at* <http://www.nih.gov/about/>, last updated on December 19, 2005.

Science and the useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." However, claim 13 of U.S. Patent No. 4,940,658 patent is not a "discovery" as that word is used in the Constitution, nor is it patentable subject matter under 35 U.S.C. § 101. Rather, it is an unpatentable law of nature.

Unlike situations in which a law of nature is merely part of a larger process, where the structure or process, when considered as a whole, is performing a function which the patent laws were designed to protect (e.g., transforming or reducing an article to a different state or thing), claim 13 of the '658 patent is nothing more than the naked patenting of a "law of nature." The Court's unbroken line of precedents preclude a finding of validity under 35 U.S.C. § 101 where a law of nature regarding a vitamin deficiency is sought to be patented in assays of any kind, whether inventive or not, when coupled with "correlating" -- *i.e.*, thinking about -- certain elevated results and vitamin deficiency. *See, e.g., Diamond v. Diehr*, 450 U.S. 175 (1981); *Parker v. Flook*, 437 U.S. 584 (1978); and *Gottschalk v. Benson*, 409 U.S. 63 (1972).

Upholding a patent centered on such "correlating" would also obliterate the protection for First Amendment activities provided by the Court's bar on the patentability of abstract ideas. The Federal Circuit's holding that physicians are culpable of direct infringement of claim 13 every time they think about or diagnose the relationship between homocysteine levels and a vitamin deficiency would have a chilling effect on protected speech and thought. Reaffirmation of this Court's precedents on the patentability of processes utilizing "laws of nature" is necessary to correct the constitutional imbalance the Federal Circuit's opinion would strike between Article I, Section 8, Clause 8 and the First Amendment of the U.S. Constitution.

Finally, upholding claim 13 of the '658 patent would have untenable policy implications. Enforcement of claim 13

will have a negative impact on medical care, the dissemination of medical information, and medical innovation. Upholding claim 13 of the '658 patent would also deter people from participating in medical research. Consequently, it is appropriate to overturn the decision of the Federal Circuit and hold invalid claim 13 of the '658 patent.

ARGUMENT

I. Background

The starting point for any analysis of patentability is the question, "What did the patent applicant invent?" *See, e.g.*, United States Patent and Trademark Office, Official Gazette Notices, November 22, 2005, Section II. With respect to claim 13 of U.S. Patent No. 4,940,658 (the '658 patent), what did the patent applicant invent? Metabolite Laboratories, Inc. and Competitive Technologies, Inc. (collectively "respondents") have not asserted that the patentee invented all methods of assaying homocysteine; in fact, clearly it did not since Abbott Laboratories invented another method, and indeed, alternate means of measuring homocysteine were available prior to the patent application and were disclosed in the patent application. Rather, what the patentee claims to have discovered is a relationship (correlation) between the levels of homocysteine and a deficiency of cobalamin or folate (vitamin deficiency). Under centuries of case law and patent policy, this relationship is an unpatentable law of nature.

The inventors in this case are physicians and scientists from non-profit institutions – Columbia-Presbyterian Medical Center, Columbia University, and the University of Colorado Health and Science Center. By analyzing blood from patients and blood donors, they observed that patients with a high level of homocysteine in their blood often had a vitamin deficiency. The inventors created a test for

measuring homocysteine levels, which is the subject of claims one through twelve of the '658 patent. Petitioner Laboratory Corporation of America Holdings (LabCorp) does not dispute that these claims are valid. It continues to pay royalties when it uses that test.

However, the inventors went further and included claim 13:

> A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> Assaying a body fluid for an elevated level of total homocysteine; and
>
> Correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

As this Court noted in its request for comment from the Solicitor General, claim 13 covers anyone who "measure[s] the level of the relevant amino acids using any device, whether the device is, or is not, patented; second, notice[s] whether the amino acid level is elevated and, if so, conclude[s] that a vitamin deficiency exists." *Laboratory Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 73 U.S.L.W. 3512, 3512 (U.S. Feb. 28, 2005). The Federal Circuit held that LabCorp induced infringement of claim 13 of the '658 patent based solely on the publication to physicians of a law of nature – the relationship between levels of homocysteine and vitamin deficiency. *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1365 (2004). Astonishingly, the Federal Circuit also held that physicians infringed claim 13 merely by thinking about the relationship between homocysteine and vitamin deficiency. *Id.* at 1363-1365.

II. Claim 13 of the '658 Patent Is Not Patentable Subject Matter and Should be Held Invalid.

A. Claim 13 of the '658 Patent Is Not a "Discovery" Within the Meaning of Article I, Section 8, Clause 8 of the U.S. Constitution.

The U.S. Constitution, Article I, Section 8, Clause 8, grants Congress the power "to promote the progress of Science and the useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries."

Throughout the '658 patent, the patentee describes its homocysteine assay (the patentability of which is not in dispute) as an "invention" and the relationship between homocysteine levels and vitamin deficiency as a "discovery."[7] However, this discovery does not rise to the level of a patentable discovery as contemplated by Article 1, Section 8, Clause 8 of the Constitution.

The term "Discoveries," as utilized in Article I, Section 8, Clause 8, is synonymous with "inventions." Writing in 1889, a patent law scholar noted that someone "may invent a machine, and may discover an island or law of nature. For doing the first of these things, the patent laws may reward him, because he is an inventor in doing it; but those laws cannot reward him for doing either of the others, because he is not an inventor in doing either." Albert A. Walker, *Text-Book of the Patent Laws of the United States of America* 2-3 (L. K. Strouse & Co., 2d ed. 1889).

> An "invention," in the parlance of the Constitution and early patent laws, is a new creation consciously sought and successfully

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[7] For example, in the "Summary of the Invention" section of the '658 patent, the relationship between homocysteine and vitamin deficiency is said to have been "discovered." U.S. Patent No. 4,940,658 col. 4, l. 17.

> reduced to practice by the inventor. A "discovery," as used in the same parlance, was intended to denote a fortuitous creation of the inventor and not merely something found by him or her. Thus, an "invention" and a "discovery" share the requirement that the inventor create something original; the difference between the two is that an "invention" is consciously sought, while a "discovery" is created unexpectedly. A discovery in that era, as used in the intellectual property law, denoted something originating from the human intellect and not merely learned by that intellect.

Linda J. Demaine and Aaron Xavier Fellmeth, *Reinventing the Double Helix: A Novel and Nonobvious Reconceptualization of the Biotechnology Patent*, 55 Stan. L. Rev. 303, 370 (2002) (citation omitted).

The dichotomy between discoveries and inventions is similarly recognized under the patent laws of other countries. The European Patent Convention (EPC) requires an "inventive step," excluding mere "discoveries" from patentable subject matter. *See* European Patent Convention, Article 52(2) (1998). The EPC states that "discoveries, scientific theories and mathematical methods" are not regarded as patentable subject material. *Id.* The similarity between Europe and the United States on this point is in keeping with the thrust toward international intellectual property harmonization.[8]

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[8] "The Uruguay round of WTO negotiations introduced TRIPS into GATT and bravely attempted to harmonize global patent systems with uniform standards of protection. . . . Both the U.S. and the U.K. have made changes to their laws in response to these provisions. . . ." Thomas K. McBride, Jr., *Patent Practice in London – Local Internationalism: How Patent Law Magnifies the Relationship of the United Kingdom with*

Claim 13 of the '658 patent does not claim a discovery as contemplated by the U.S. Constitution, Article I, Section 8, Clause 8; therefore, claim 13 should be held invalid. The relationship between homocysteine levels and vitamin deficiency is a law of nature that exists independent of human intervention, invention, or manipulation. This relationship existed in mammals long before it was uncovered, so this correlation is not a new or an inventive innovation, but only the description of existing natural phenomenon, a law of nature. While "anything under the sun that is made by man" might be patentable, *Diamond v. Diehr*, 450 U.S. 175, 182 (1980) (citation omitted), the relationship of homocysteine to vitamin deficiency was not made by man.

Moreover, recognition of claim 13 of the '658 patent would also be contrary to the policies underlying Article I. The underlying goal of Article I, Section 8, Clause 8 was to "promote the progress of Science and the useful Arts," a goal that is not met in the case of a patent that restricts others from using a law of nature in their inventions.

B. Claim 13 of the '658 Patent Operates as an Unpatentable "Law of Nature" Under 35 U.S.C. § 101.

35 U.S.C. § 101 limits the categories of inventions that are patentable, stating "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title." This Court has consistently held that laws of nature are not patentable. "This Court has undoubtedly recognized limits to § 101 and every discovery is not embraced within the statutory terms.

Europe, the United States and the Rest of the World, 2 Loy. U. Chi. Int'l L. Rev. 31, 47 (2004-2005).

Excluded from such patent protection are laws of nature, natural phenomena, and abstract ideas." *Diehr*, 450 U.S. at 185. *See also Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980); *Parker v. Flook*, 437 U.S. 584 (1978); *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972); *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948); *O'Reilly v. Morse*, 56 U.S. (15 How.) 62, 116 (1853); *Le Roy v. Tatham*, 55 U.S. (14 How.) 156, 175 (1852).

This Court has pointed out that a scientific principle "reveals a relationship that has always existed." *Flook*, 437 U.S. at 593.[9] Consequently, "[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." *Benson*, 409 U.S. at 71-72. In *Funk Bros.*, 333 U.S. at 130-131, the Court recognized that unpatentable laws of nature include biological phenomenon affecting naturally-occurring living organisms and held invalid a patent on a mixed culture of bacteria for use in the inoculation of seeds. While noting that the discovery was "ingenious," the Court held, "He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes." *Id.* at 130.

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[9] This logic is also underscored by the inherency doctrine in patent law. For example, in a 2002 case, the Federal Circuit held that a patent cannot be granted to an applicant who has discovered a natural attribute of a living entity. *In re Cruciferous Sprout Litigation*, 301 F.3d 1343 (Fed. Cir. 2002). In that case the Federal Circuit stated, "[T]he glucosinolate content and Phase 2 enzyme-inducing potential of sprouts necessarily have existed as long as sprouts themselves, which is certainly more than one year before the date of application . . . ." *In re Cruciferous Sprout Litigation*, 301 F.3d at 1350. Similarly, in the case at bar, the inventors did not create the relationship between homocysteine and vitamin deficiency. That relationship, like the enzyme-inducing potential of certain sprouts or the strength of pure tungsten (*see General Electric Co. v. DeForest Radio Co.*, 28 F.2d 641, 643 (3d Cir. 1928), *cert. denied* 278 U.S. 656 (1929)), previously existed in nature.

There are good policy reasons for not granting a patent applicant a patent on a law of nature. The Court in *Morse*, 56 U.S. (15 How.) at 113, expressed its concern that granting Samuel Morse broad rights to a law of nature for a generic purpose (the use of electromagnetic waves to write at a distance) beyond its particular application in Morse's concrete novel invention (the telegraph) would overcompensate the inventor by giving him rights to subsequent inventions that he himself did not create that used the law of nature governing electromagnetic waves. The Court was also concerned that such a large grant of rights would deter other inventors to the public's detriment. *Id* at 120-121.

The Court denied Morse's broad patent claim, stating:

> If this claim can be maintained, it matters not by what process or machinery the result is accomplished. For aught that we now know some future inventor, in the onward march of science, may discover a mode of writing or printing at a distance by means of the electric or galvanic current, without using any part of the process or combination set forth in the plaintiff's specification. His invention may be less complicated -- less liable to get out of order -- less expensive in construction, and in its operation. But yet if it is covered by this patent the inventor could not use it, nor the public have the benefit of it without the permission of this patentee.

Id. at 113.

The Court's concern in *Morse* has come to pass in this case. Abbott Laboratories invented an alternative test for homocysteine levels that can be performed more efficiently, but use of it to assess the likelihood of vitamin deficiency is an infringement of the overly-broad patent claim 13 under

the logic of the Federal Circuit's decision. This holding gives patent rights not only to the test that the '658 patent inventors themselves patented, but to any test invented by anyone else that makes use of the law of nature about the relationship between elevated homocysteine levels and vitamin deficiency, even if that other test is more reliable, less expensive, simpler in use or operation, or performed by a new machine.[10]

C. Claim 13 of the '658 Patent Is Distinguishable From an Allowable Patent Claim Which Merely Incorporates a Law of Nature in a Larger, Patentable Process.

Despite the patentee's attempt to couch the claim as a two-step process, claim 13 is a naked patent claim on a law of nature and not a process within the meaning of 35 U.S.C. § 101. A process, as described by this Court in *Cochrane v. Deener*, 94 U.S. 780 (1877), and reaffirmed in *Diehr*, is a "mode of treatment of certain materials to produce a given result. It is an act, or a series of acts, performed upon the subject-matter to be transformed and reduced to a different state or thing." *Diehr*, 450 U.S. at 183 (quoting *Cochrane*, 94 U.S. at 788). The Court in *Diehr* stated further, "transformation and reduction of an article 'to a different state or thing' is the clue to the patentability of a process claim that does not include particular machines." *Id.* at 184 (quoting *Benson*, 409 U.S. at 70).

It is undisputed that there is no "particular machine" to be utilized in claim 13. Nor can it be seriously maintained that there is a "transformation and reduction of an article to a

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[10] While Metabolite might argue that an alternative homocysteine test could be used without infringing claim 13 if the physician using the test does not then think about the relationship of the test results of vitamin deficiency, Metabolite's own witness, one of the inventors of the '658 patent, said physicians would necessarily think about that relationship or risk a malpractice lawsuit. *Metabolite Labs., Inc.*, 370 F.3d at 1364.

different state or thing" where any test, transforming or not, can provide the data that is called for by the first step.

Even if it could be shown that transforming is a necessary feature of all "assays," even those yet to be invented, it is clear that any such transformation is not the essence of the purported process in claim 13 as it was in *Diehr*. There the patentee transformed raw rubber into a final product usable by consumers. Transformation was the point of the process. Here, the acquisition of data, *i.e.*, the number representing the patient's homocysteine level, is the sole purpose of the first step. The mere gathering of data to apply a mathematical formula should not make the formula patentable, in the same way that inconsequential postsolution activities cannot convert an unpatentable principle into a patentable process. *Flook*, 437 U.S. at 590. Since the second step of claim 13 is merely a mental step, a conclusion based upon the scientific principle that elevated homocysteine levels mean vitamin deficiency in a certain percentage of the cases,[11] there is no process here. Data is gathered, and in a physician's mind a scientific principle is applied and a conclusion is drawn. That is all.

In addition, the file wrapper history in this case should estop Metabolite from claiming that claim 13 covers a two-step process. The history of this case shows an attempt to claim the use of a law of nature in a sweeping range of technologies as was prohibited in the *Morse* case. The patentee originally resisted adding a discrete separate step for claim 13 that would reveal enablement under 35 U.S.C. § 112, with the stunning party admission as follows:

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[11] According to a study of 7,747 patients in the '658 patent, the percentage of patients with vitamin deficiency accurately predicted by the test of homocysteine is 89%. Eleven percent of people with the vitamin deficiency are missed by the test. Moreover, 12% of healthy people on whom the homocysteine test and correlation are used will erroneously be told they have a vitamin deficiency. Because the test is not perfect, it is important not to deter subsequent innovation.

> "[A]s applicants are the first to detect cobalamin or folate deficiency by assaying body fluids for total homocysteine, it is believed that they are entitled to a claim of equivalent scope, *not limited to any particular steps or methods*."

Metabolite, 370 F.3d at 1362 (emphasis added).

Since step 1 of claim 13 specifies *any* kind of assaying for an elevated level of total homocysteine, and thus does not involve an inventive aspect, the Federal Circuit focused on step 2, "[t]he correlating step [which] is a simple conclusion that a cobalamin/folate deficiency exists *vel non* based on the assaying step. The patentee did not conceal or fail to disclose this correlation, but instead featured it as the centerpiece of the invention." *Id.* at 1367. Moreover, "the record shows repeatedly that the correlating step is well within the knowledge of one of skill in this art." *Id.* In short, there is no valid process patent when the applicant admits there is no process to begin with.

Patent law does not allow for exclusive control over a law of physiology, even if such a natural phenomenon is observed in a blood draw. Adding a "correlating" step to a process that is devoid of any other inventive step or aspect does not change that result. Moreover, thinking about a physiological principle is not a "process" or "method" or "art" under patent law. Rather, it is core First Amendment activity, unpatentable ideation.

However, assuming *arguendo* that the Court finds that claim 13 constitutes a "process," that process is more analogous to the processes found not to be patentable in *Benson* and *Flook* than to the *Diehr* process.

Benson and *Flook* hold that the process itself must be new and useful because the law of nature (or, in those cases, the mathematical algorithm) "whether known or unknown at the time of the claimed invention, [is]... one of the 'basic tools of scientific and technological work,' see *Gottschalk v.*

Benson, 409 U.S. at 67, and is treated as though it were a familiar part of the prior art." *Flook*, 437 U.S. at 591-92.

Under the standards of *Benson* and *Flook*, neither of the steps of claim 13 present an inventive aspect. Step one, the assay, fails because there is not a specific new and useful process involved. Rather, the patentee claims all assays for homocysteine, no matter what kind and no matter who actually invented the assay, without any means of enablement for the assays claimed. The second step, the application of the correlation, fails because it is merely the naked application of a law of nature, which is a basic tool of scientific work.

This contrasts greatly with the patentable process using a mathematical formula in *Diehr*. That was a specific process involving multiple steps,[12] involving a particular machine,

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[12] There were three claims at issue in *Diehr*, 450 U.S. at 179. The first claimed:

> 1. A method of operating a rubber molding press for precision molded compounds with the aid of a digital computer, comprising:
>
> 'providing said computer with a data base for said press including at least,
>
> 'natural logarithm conversion data (ln),
>
> 'the activation energy constant (C) unique to each batch of said compound being molded, and
>
> 'a constant (x) dependent upon the geometry of the particular mold of the press,
>
> 'initiating an interval timer in said computer upon the closure of the press for monitoring the elapsed time of said closure,
>
> 'constantly determining the temperature (Z) of the mold at a location closely adjacent to the mold cavity in the press during molding,
>
> 'constantly providing the computer with the temperature (Z),
>
> 'repetitively calculating in the computer, at frequent intervals during each cure, the Arrhenius equation for reaction time during the cure, which is
>
> 'ln v <v1>equ CZ+x
>
> 'where v is the total required cure time,

used for a specific application. In *Diehr*, this Court distinguished between process claims containing scientific principles "where the structure or process, when considered as a whole, is performing a function which the patent laws were designed to protect (e.g., transforming or reducing an article to a different state or thing)", 450 U.S. at 192, and those which are "seeking patent protection for [a] formula in the abstract," aided by a competent draftsman. *Id.* at 191.

Claim 13 of the '658 patent does not seek patent protection for the patentee's assay for homocysteine levels. That protection is claimed by other claims in the patent and is not here in dispute. What then does claim 13 add to the other claims? The answer is obviously the protection of the discovery of the relationship between elevated homocysteine levels and vitamin deficiency. Is this discovery the type that the patent laws were designed to protect? No, since it is most clearly a law of nature. By adding a step of using any means of gathering data, whether patentable or not, to apply in a law of nature, does the process as a whole become something the patent laws were designed to protect or is it still just the law of nature, claimed through a clear subterfuge of a competent draftsman? All laws of nature require the input of data to apply the law. Hence, any such law could be drafted as a two or three step process, e.g. obtain a reading for x, apply the law that x = y, conclude y.

This purported process contains none of the touchstones this Court has used to winnow properly protectable process claims from the overreaching claims of those who discovered natural laws and sought to monopolize them. It does, however, contain a cleverly drafted breakdown of a one-step scientific principle into a purported two-step process. It is

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'repetitively comparing in the computer at said frequent intervals during the cure each said calculation of the total required cure time calculated with the Arrhenius equation and said elapsed time, and

'opening the press automatically when a said comparison indicates equivalence.'

precisely the type of claim this Court sought to prevent in *Benson* and *Flook*.

Moreover, the Federal Circuit ruled that claim 13 of the '658 patent is infringed simply by a physician thinking in his or her head after receiving the results of a body fluid assay that the level of homocysteine is or is not correlated to a vitamin deficiency of cobalamin or folate. *Metabolite Labs., Inc.*, 370 F.3d at 1363-1365. This thought process proceeds entirely inside the physician's head and is essentially, a physician applying a biological fact to his patient. The physician's mere thoughts were found to be infringement. Yet, mental processes have specifically been ruled by the Supreme Court to be unpatentable subject matter in *Benson*, 409 U.S. at 67, and *Flook*, 437 U.S. at 589, so this step alone cannot serve as a basis to uphold claim 13.

The potential harms to the public in upholding an inappropriate claim on a law of nature involving a medical fact are particularly grave. Erroneously granted patents on computer programs or a business method are unlikely to kill someone. Discouraging physicians from learning about or thinking about a medical fact could.

III. Patent Protection for Claim 13 of the '658 Patent Chills the Exercise of First Amendment Rights.

Both the patent law and the First Amendment have a common goal: to encourage the expansion of knowledge through disclosure. The patent law encourages disclosure of inventions to seed future innovation in the technological sphere. *See, e.g. Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 151 (1989) ("the ultimate goal of the patent system is to bring new designs and technologies into the public domain through disclosure"). The First Amendment encourages a marketplace of ideas. U.S. Const., amend. I.

When the U.S. Patent and Trademark Office grants a patent that can be used to prohibit a physician from thinking

about a medical fact, and prohibits anyone other than the patent holder from publishing that medical fact, First Amendment values are implicated.

A. Claim 13 of the '658 Patent Chills the Exercise of Freedom of Thought.

Certain rights are inherent in the expressly enumerated rights of speech and the press and must be preserved to effectuate the principles of the First Amendment. For example, this Court has consistently recognized the importance of freedom of thought, the ability to form or hold a belief prior to its expression, as a right inherent in the First Amendment. *See Wooley v. Maynard*, 430 U.S. 705, 714-715 (1977); *Palko v. Connecticut*, 302 U.S 319, 326-327 (1937). This is in keeping with precedents recognizing that the First Amendment protects other activities which are precursors necessary to the formulation of expression, communication and publication. *Richmond Newspapers v. Virginia*, 448 U.S. 555, 556 (1980); *Globe Newspaper Co. v. Superior Court*, 457 U.S. 596, 604 (1982).

Freedom of thought is a fundamental right necessary for the existence of freedom of speech and of the press. "The guarantee of free expression...is inextricably linked to the protection and preservation of open and unfettered mental activity." Laurence Tribe, *American Constitutional Law* § 15-7, at 1322 (2d ed. 1988). As Justice Cardozo stated, "freedom of thought...is the matrix, the indispensable condition, of nearly every other form of freedom. With rare aberrations a pervasive recognition of that truth can be traced in our history, political and legal." *Palko*, 302 U.S. at 326-327.

In this case, the Federal Circuit stated that "the parties hinge the direct infringement issue solely on whether the physicians perform the correlating step," *Metabolite Labs., Inc.*, 370 F.3d at 1364, even though that correlation was done entirely in the physicians' minds. Thus, the Federal Circuit

held that the physicians directly infringed Metabolite's claim 13 by thinking that a homocysteine level may signify a vitamin deficiency. Consequently, the granting and enforcement of claim 13 chills the exercise of freedom of thought.

The progress of scientific achievement is imperiled when a patent claim such as claim 13 asserts as private intellectual property basic scientific information. Because of the enforcement of claim 13, physicians in clinics and in research institutions will be prohibited from thinking about the correlation between elevated levels of homocysteine and vitamin deficiency unless they pay the toll of using Metabolite's test.

B. Claim 13 of the '658 Patent Chills the Exercise of Freedom of Speech.

The Federal Circuit held that LabCorp indirectly infringed claim 13 of the '658 patent by publishing basic scientific information. *Id.* at 1364-65. Such a holding chills the exercise of freedom of speech. This result denies physicians hoping to treat ill patients access to basic scientific information and restricts the ability of other scientists to undertake further research regarding the information and publish the results of that research.

The slim reason why over $4 million in damages were assessed against LabCorp was that they induced infringement by publishing an article about the homocysteine-vitamin deficiency relationship. But it is difficult to imagine how the publication of a previously-known and previously-published fact could be found to have induced infringement. Arguably, LabCorp did not induce infringement when it informed physicians about the relationship between homocysteine levels and vitamin deficiency because physicians already knew about that relationship. In fact, the association is so well-known that one of the inventors said it would violate the standard of care for physicians not to apply that known

association.[13] The '658 patent itself revealed the association. At least 22 articles in the medical literature written by the inventors themselves before the publication of the LabCorp article disclosed the correlation.[14] In addition, other physicians and scientists published articles in the medical literature revealing that correlation.[15]

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[13] The inventor said "that it would be malpractice for a physician to receive a total homocysteine assay without determining cobalamin/folate deficiency." *Metabolite*, 370 F.3d at 1364.

[14] A search of www.pubmed.gov, which is a search engine provided by the National Center for Biomedical Information, the National Library of Medicine, and the National Institute of Health created to disseminate biomedical information, located 22 articles that disclosed the homocysteine and vitamin deficiency correlation prior to the date Laboratory Corporation of America distributed its publication of the correlation to physicians. *See e.g.*, A.M. Kuzminski et al., *Effective Treatment of Cobalamin Deficiency with Oral Cobalamin*, 92 Blood 4, 1191-98 (1998); A.E. Sumner et al., *Elevated Methylmalonic Acid and Total Homocysteine Levels Show High Prevalence of Vitamin B_{12} Deficiency After Gastric Surgery*, 124 Ann. Intern. Med. 5, 469-76 (1996); J. Lindenbaum et al., *Prevalence of Cobalamin Deficiency in the Framingham Elderly Population*, 60 Am. J. Clin. Nutr. 1, 2-11 (1994); D.G. Savage et al., *Sensitivity of Serum Methylmalonic Acid and Total Homocysteine Determinations for Diagnosing Cobalamin and Folate Deficiencies*, 96 Am. J. Med. 3, 239-46 (1994); S.P. Stabler et al., *Elevation of Total Homocysteine in the Serum of Patients with Cobalamin or Folate Deficiency Detected by Capillary Gas Chromography-Mass Spectrometry*, 81 J. Clin. Invest. 2, 466-74 (1988).

[15] *See e.g.*, H. Ono et al., *Plasma Total Homocysteine Concentrations in Epileptic Patients Taking Anticonvulsants*, 46 Metabolism 8, 959-62 (1997); S.E. Miner et al., *Clinical Chemistry and Molecular Biology of Homocysteine Metabolism: An Update*, 30 Clin. Biochem. 3, 189-201 (1997); E. Joosten et al., *Is Metabolic Evidence for Vitamin B-12 and Folate Deficiency More Frequent in Elderly Patients with Alzheimer's Disease?*, 52 J. Gerontol A. Biol. Sci. Med. Sci. 2, M76-9 (1997); J. Metz et al., *The Significance of Subnormal Serum Vitamin B_{12} Concentration in Older People: A Case Control Study*, 44 J. Am. Geriatr. Soc. 11, 1355-61 (1996); Jensen M. Krogh et al., *Folate and Homocysteine Status and Haemolysis in Patients Treated with Sulphasalazine for Arthritis*, 56 Scan J. Clin. Lab. Invest. 5, 421-9 (1996); E. Joosten et al., *Cobalamin Absorption and Serum Homocysteine and Methylmalonic Acid in Elderly*

By prohibiting further publication of the homocysteine-vitamin deficiency relationship, enforcement of claim 13 runs afoul of this Court's First Amendment holdings that "the state may not, consistently with the spirit of the First Amendment, contract the spectrum of available knowledge." *Griswold v. Connecticut*, 381 U.S. 479, 482 (1965).

IV. Allowing Claim 13 of the '658 Patent to Stand as Valid Would Have Untenable Policy Implications.

A. Upholding Claim 13 of the '658 Patent Would Have a Negative Impact on Health Care in the U.S.

The enforcement of claim 13 of the '658 patent creates a patent infringement when a physician thinks about a law of nature, a medical fact. There is no fair use exception, unlike in copyright law. 17 U.S.C. § 107. There is only a very narrow research exception, so narrow as to be declared by commentators as "for all practical purposes a nullity." Janice M. Mueller, *The Evanescent Experimental Use Exemption from the United States Patent Infringement Liability: Implications for University and Nonprofit Research and Development*, 56 Baylor L. Rev. 917, 962 (2004). *See also* Katherine J. Strandburg, *What Does the Public Get? Experimental Use and the Patent Bargain*, 2004 Wis. L. Rev. 81, 87 (2004); *Madey v. Duke Univ.*, 307 F.3d 1351, 1362 (Fed. Cir. 2002). This contrasts with the broad experimental use exceptions in other countries. Gen'l Secretariat of the Council of the Eur. Communities, Records of the Luxembourg Conference on the Community Patent 1973, art. 31(b), at 302; *see also* William R. Cornish, *Experimental Use of Patented Inventions in European Community States*, 29 Int'l Rev. Indus. Prop. & Copyright L. 735, 735-36 (1998),

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Subjects with Low Serum Cobalamin, 51 Eur. J. Haematol. 1, 25-30 (1993).

Scrutiny of claim 13 of the '658 patent is particularly important because it can affect people's health. Vitamin deficiency is a major-public health problem. It "can cause serious illnesses in humans, including vascular disease, cognitive dysfunction, birth defects and cancer. If detected early enough, however, vitamin supplements readily treat the deficiency." *Metabolite Labs., Inc*, 370 F.3d. at 1358.

If claim 13 of the '658 patent is declared valid, patients' medical care will suffer. Physicians (other than those who have ordered a test from the patent holder) will be deterred (on penalty of patent infringement) from recognizing in their patients the association between the level of homocysteine and vitamin deficiency. It will also impede health care if, every time a health care provider or medical laboratory technician is about to diagnose a patient, he or she has to stop, mid-thought, and undertake an extensive patent search.[16]

International conventions about intellectual property rights, to which the United States is a signatory, provide that patent rights should give way to health concerns in certain instances. For example, the Agreement on Trade Related Aspects of Intellectual Property Rights of the World Trade Organization, promulgated in 1995, highlights how public health can be given greater weight than the commercial concerns of patentees. Agreement on Trade-Related Aspects of Intellectual Property Rights, Dec. 15, 1993, 33 I.L.M. 81 (1994) (hereinafter TRIPS). Article 27 of TRIPS specifically

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[16] Since the medical fact might, as in the case under consideration, have been patented prior to 1996, physicians will have to do patent searches for all medical facts, even though ultimately some physicians might be protected by the limited safe harbor for physicians under 35 U.S.C. § 287(c). Even with respect to post-1996 patents, however, the protection of § 287 will not apply to other individuals who supply medical information, such as a Ph.D. in genetics who applies a medical correlation about a particular gene mutation and breast cancer, or a group that publishes medical information, such as the People's Medical Society.

allows governments to exclude from patentability diagnostic, therapeutic, or surgical methods. *Id.*

The enforcement of claim 13 of the '658 patent increases the cost of health care and impedes appropriate medical care by improperly interfering with physicians' and patients' ability to gain information about a medical fact and to think about that fact.

B. Upholding Claim 13 of the '658 Patent Would Have a Negative Impact on the Dissemination of Medically Relevant Information.

The enforcement of claim 13 of the '658 patent interferes with the free flow of information about a scientific fact of great relevance to the health of individuals. In this case, the offending publication provides just the sort of information that health care providers and consumers need – information about both the diagnosis and treatment of vitamin deficiency. *Metabolite*, 370 F.3d at 1365. If claim 13 is upheld, entities that wish to publish information about the relationship between homocysteine and a vitamin deficiency – a true medical fact – will be deterred from doing so by the cost of patent royalties or the possibility of millions of dollars in damages for induced infringement.

The absurdity of Metabolite's position in this case is illustrated by the following example: it would not induce infringement of claim 13 if the People's Medical Society published an article saying, "There are several tests for homocysteine levels. We recommend that you get the test from Abbott Laboratories." However, if People's Medical Society attempted to further its non-profit mission by providing information to consumers and added, "An elevated level on a homocysteine test can indicate whether you have vitamin deficiency," that statement would induce infringement of the patent. Clearly, claim 13 deters publication of medical information.

Upholding claim 13 of the '658 patent would also create an incentive for other companies to assert patent rights over other scientific facts, further increasing the cost of health care and diminishing the flow of medical information.

C. Upholding Claim 13 Would Have a Negative Impact on Innovation.

Patent law has one underlying policy aim -- to encourage innovation. The mechanism by which that is achieved is by granting the patent holder a monopoly on any use of the patented invention in exchange for a disclosure in the patent application of how exactly the invention can be made. This encourages innovation by stimulating people to invent in the first place, often by making a better, cheaper, more interesting, and more effective alternative to an existing invention. Thus, if a person patents a mousetrap made of wood, when the patent application later becomes public (a condition of the patent grant), other inventors can read about how the inventor made the mousetrap and can create novel variations using significantly different materials or processes. *See Graham v. John Deere Co.*, 383 U.S. 1, 8-9 (1966).

Here, claim 13 deters innovation by preventing researchers from thinking about or further exploring the relationship of homocysteine and vitamin deficiency. Even though another inventor could create a better homocysteine test, perhaps one with a 99% correlation rather than the 89% correlation of the Metabolite test, that inventor would not be able to make his better test available because users of the test would invariably think that the homocysteine levels measured by the test were related to vitamin deficiency.

By chilling the publication of information about the relationship between homocysteine levels and vitamin deficiency, claim 13 will operate to deter researchers from developing treatments for vitamin deficiency. In fact, if a potential funder of research into treatments for vitamin deficiency described the homocysteine-vitamin deficiency

relationship in a published solicitation for research proposals, it could be liable for inducing infringement.

D. Upholding Claim 13 Would Deter People From Participating in Medical Research.

Many patients served as research subjects and gave generously of themselves so that the inventors of the '658 patent could recognize an inherent biological phenomenon, the law of nature that high homocysteine levels correlate with vitamin deficiency. According to the '658 patent, at least 301 of these patients were subjected to full clinical evaluations including risky neurological evaluations, blood and bone marrow smears, and repeated serum tests for antibodies to intrinsic factor for a period of two years. In all, 7,987 patients were studied and tested to discover the patented relationship between homocysteine and vitamin deficiency. There is no evidence in the patent or in the publications by the inventors that the patients were informed that medical information from their bodies would be patented.[17]

Upholding claim 13 is likely to have a deterrent effect on people's willingness to participate in research. Why should someone altruistically give of their time and subject themselves to potential physical risks if this leads to a patent on a medical fact, increasing health care costs and deterring innovation? As a result of this case, patients who are potential research subjects are aware now that their altruistic

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[17] Case law and medical ethics underscore the importance of such disclosures. *See, e.g., Moore v. Regents of the University of California*, 51 Cal.3d 120, 793 P.2d 479 (1990). The AMA Code of Ethics Section 2.08 (3), provides "Human tissue and its products may not be used for commercial purposes without the informed consent of the patient who provided the original cellular material." American Medical Association, Council on Ethical and Judicial Affairs, *Code of Medical Ethics: Current Opinions with Annotations*, Section 2.08 Commercial Use of Human Tissue (Chicago: AMA, 2000).

participation in research, often at the cost of physical pain and risk, might lead to medical facts being patented which would increase the cost of their health care and interfere with its quality. This is exactly what happened to the 7,987 people who participated in this study, some of whom had painful bone marrow fluid extractions without knowing that the law of nature discovered in their bodies would be patented. It would be reasonable for people to lose interest in being research subjects if the laws of nature discovered in their bodies lead to patents that can be enforced to their detriment.

E. Adherence to the Law of Nature Doctrine Will Not Stifle Innovation.

The Court should not forsake its strict adherence to its laws of nature non-patentability doctrine which is of constitutional as well as statutory dimension. Both Article I, Section 8, Clause 8 and the First Amendment provide breathing room for the public domain of abstract ideas and speech related to such a marketplace of ideas. Some *amici curiae* might argue that adhering to the laws of nature doctrine will stifle innovation, but that is unlikely. With the laws of nature doctrine in place, this has been the most innovative era in the nation's history. Moreover, similar fears of discouragement of innovation voiced to the Court by the computer software industry during the *Benson* litigation were wisely directed to Congress, and have since proven to be misplaced. To the extent that the biotechnology sector now wants to exempt itself from longstanding legal precedent and to codify the Federal Circuit's holding in this case, that sector should also go first to Congress, to the extent such an approach is not constitutionally futile. Whether applied to new or old technology, the Court's non-patentability of laws of nature doctrine should be applied to all sectors with the same "general strictness." *Cf. Graham*, 383 U.S. at 19 (1966); *Chakrabarty*, 447 U.S. at 309, 315-316.

CONCLUSION

Metabolite's success in transmuting the Patent Act into an exclusive governmentally-issued license to preclude physicians, health care publishers, bioscience researchers, and citizens alike from merely thinking about a principle of human physiology underscores the importance of the issue presented. Upholding claim 13 of the '658 patent would be in conflict with patent jurisprudence and First Amendment values and is likely to retard, not promote, "the progress of Science and the useful Arts." The Court should reaffirm its rule that one cannot patent "laws of nature, natural phenomena, and abstract ideas," *Diehr*, 450 U.S. at 185, even if the patent applicant attempts to lay claim to such a law of nature by fractionating a single claim to make it appear that it relies on two, three, or more steps, where the only alleged innovation in the various steps and process is a law of nature. We urge the Court to reverse the Federal Circuit decision in this case.

Respectfully submitted,

LORI B. ANDREWS
Counsel of Record
DEBRA GREENFIELD
CLEMENTS RIPLEY
CHICAGO-KENT COLLEGE OF LAW
565 West Adams Street
Chicago, IL 60611
Tel: 312-906-5359

FRANCIS C. J. PIZZULLI
718 Wilshire Boulevard
Santa Monica, CA 90401
Tel: 310-451-8020

Counsel for Amicus Curiae

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In The
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LABORATORY CORPORATION OF AMERICA HOLDINGS (DOING BUSINESS AS LABCORP),

Petitioner,

v.

METABOLITE LABORATORIES, INC. AND COMPETITIVE TECHNOLOGIES, INC.,

Respondents.

On Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

BRIEF FOR *AMICI CURIAE* PERLEGEN SCIENCES, INC. AND MOHR, DAVIDOW VENTURES IN SUPPORT OF RESPONDENTS

GIDEON A. SCHOR
Counsel of Record
MEREDITH E. KOTLER
VERN NORVIEL
ERIC H. WITT
WILSON SONSINI GOODRICH & ROSATI
PROFESSIONAL CORPORATION
12 East 49th Street, 30th Floor
New York, NY 10017
(212) 999-5800

Counsel for Amici Curiae

COCKLE LAW BRIEF PRINTING CO. (800) 225-6964
OR CALL COLLECT (402) 342-2831

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INTEREST OF *AMICI CURIAE*[1]

Amicus Perlegen Sciences, Inc. ("Perlegen") is a leader in personalized medicine, working to provide safe and effective medications to patients worldwide. The company quickly and cost effectively analyzes millions of unique genetic variations in patients to explain and predict the efficacy and adverse effect profiles of prescription drugs. For example, if a sub-group of patients is resistant to, or adversely affected by, a drug, the company can determine the genetic basis for such resistance or adverse effect, and thereby identify the population for whom the drug would be both safe and effective. The company also applies this expertise to discovering genetic variants associated with disease and thereby pave the way for new therapeutics and diagnostics. Through its rapid ability to examine entire genomes, Perlegen is attempting to bring drugs to market whose clinical development would otherwise have been discontinued and to find the genetic associations with drug response and disease that improve patient care.

Perlegen has a strong interest in ensuring that claim 13 ("Claim 13") of U.S. Patent No. 4,940,658 (the "'658 patent") is held to recite patentable subject matter. A holding that the diagnostic method identified in Claim 13 is unpatentable could significantly diminish Perlegen's incentive to engage in research and to develop diagnostic

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[1] Counsel for all parties have consented to the filing of this brief, and their consents have been lodged with the Clerk of this Court. No counsel for any party had any role in authoring this brief, and no person other than the named *amici* and their counsel has made any monetary contribution to the preparation and submission of this brief. *See* Rule 37.

methods for determining the patient population for which particular drugs are safe and effective.

Amicus Mohr, Davidow Ventures ("MDV") is a leading Silicon Valley-based venture capital firm specializing in predictive diagnostics and personalized medicine, as well as other areas that are dependent on fundamental innovation and invention. MDV works closely with life sciences entrepreneurs from academic institutions, like Stanford, Harvard, and MIT, who are passionate about inventing and commercializing novel technologies and business models that will transform the practice of medicine for the benefit of the ultimate consumers – physicians and patients. With its strong multidisciplinary scientific expertise, MDV brings 20 years of experience helping entrepreneurs build start-ups, and close involvement with industry and academic leaders in multiple health-care disciplines.

Like Perlegen, MDV has a strong interest in ensuring that Claim 13 is held to recite patentable subject matter. MDV believes that the health-care industry is on the cusp of a transformation in which more informative, personalized diagnostics will serve as a gateway to better, more efficient treatment and significantly reduce the waste and (all too frequently) loss of life associated with treatment of patients based on too little information. MDV has provided funding for a number of these next-generation diagnostics start-ups, in part in the knowledge that diagnostic methods similar to those set forth in Claim 13 have been consistently granted patent protection over an extended period of time. Any other holding with respect to Claim 13 could limit the economic viability of companies seeking to research and develop diagnostic methods like that identified in Claim 13, and thus could adversely affect the life

sciences companies for which MDV has provided investment backing. Moreover, if such methods are held unpatentable, MDV – indeed, venture capitalists in general – would have significantly diminished incentives to invest in the very companies that are on the forefront of research and development in personalized medicine and diagnostics.

SUMMARY OF ARGUMENT

Claim 13 recites patentable subject matter under 35 U.S.C. § 101. To satisfy the patentability test of § 101, a process claim must, when considered as a whole, identify subject matter that is useful and made by man, that is not simply a natural law, and that transforms a physical object into a different state or thing. That one step in a process may be unpatentable as a law of nature does not prevent the process itself from being patentable under § 101. Claim 13, which recites an assay-plus-correlation method for diagnosing cobalamin and folate deficiencies, easily satisfies these requirements.

Claim 13 as a whole performs a useful function – employing body fluid to diagnose these two deficiencies – that neither the assay step nor the correlation step alone could perform. This diagnostic tool is made by man because, in nature, it is impossible to diagnose such deficiencies through unaided inspection of body fluid. Even assuming that the correlation step is a natural law, the result of the process, a medical diagnosis, is not. The method identified in Claim 13 also transforms body fluid through physical and chemical alteration so that it may be injected into scientific instruments for measurement.

Because Claim 13 is self-limited to assays of body fluid, not body tissue, it does not preempt every substantial application of the asserted natural law. If this Court holds the subject matter of Claim 13 to be unpatentable, the validity of a vast number of well-known diagnostic patents – including tests for prostate cancer and HIV – would be in question, because all such tests involve, literally or substantively, a similar assay-plus-correlation method.

Should this Court nonetheless hold the subject matter of Claim 13 to be unpatentable, its holding should be narrow. This Court's cases extensively discuss patentable subject matter and already set appropriate limits on the scope of patentability. Any ruling in this case should not fundamentally alter those limits, particularly where, as here, the record is not fully developed, and any concern of the Court could be addressed by a more limited reading of "correlation" or by a minor modification of Claim 13.

A holding that Claim 13 does not recite patentable subject matter could upset the careful balance struck by Congress in the nation's patent laws. Granting patent protection for diagnostic-method claims creates strong incentives for research and development, while providing the public, and competing researchers and companies, with full mandatory disclosure concerning the patent's underlying details. Such disclosure can help, even spur, competitors to develop new improvements and methods. Without that incentive, researchers, companies, and investors will be unlikely to put their time and money into research and development of new diagnostic methods.

ARGUMENT

I. CLAIM 13'S COMBINATION OF THE ASSAY STEP WITH THE CORRELATION STEP IS PATENTABLE SUBJECT MATTER, EVEN ASSUMING THAT THE CORRELATION STEP ALONE IS NOT PATENTABLE

A. Claim 13 Recites Patentable Subject Matter

"[T]hat one or more of the steps in [a] process may not, in isolation, be novel or independently eligible for patent protection is irrelevant to the question of whether the claim[] as a whole recite[s] subject matter *eligible* for patent protection under § 101."[2] *Diamond v. Diehr*, 450 U.S. 175, 193 n.15 (1981) (emphasis in original). While a law of nature is not patentable, "a process is not unpatentable simply because it contains a law of nature." *Parker v. Flook*, 437 U.S. 584, 590 (1978). "It is now commonplace that an *application* of a law of nature . . . to a known . . . process may well be deserving of patent protection." *Diehr*, 450 U.S. at 187 (emphasis in original). The key is whether a useful invention has resulted: "He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes. If there is to be invention from such discovery, it must come from the application of the law of nature to a new and useful end." *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948).[3] A combination of old or otherwise unpatentable

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[2] Claim 13, in identifying a "method," *see* SA 30, is a process claim. *See* 35 U.S.C. § 100(b) (defining "process" as, *inter alia*, "method").

[3] Although *Funk Bros. Seed Co.* concerned a product claim, its holding applies to a process claim. *See Diehr*, 450 U.S. at 188 n.11 (citing *Gottschalk v. Benson*, 409 U.S. 63, 68 (1972)). As a general matter, cases that respectively concern product and process claims may be cited interchangeably for the purpose of determining whether the

(Continued on following page)

elements can itself be patentable when "the whole in some way exceeds the sum of its parts." *Great Atl. & Pac. Tea Co. v. Supermarket Equip. Corp.*, 340 U.S. 147, 150-52 (1950).

Claim 13's combination of the assay and correlation steps is indisputably a useful invention, because it performs a function that neither step alone can perform. Neither of Claim 13's two steps can use body fluid to diagnose cobalamin or folate deficiency. Prior to the invention of the method recited in Claim 13, the assay step could result only in a determination of the level of a chemical substance, homocysteine, in the assayed body fluid. But that assay result was diagnostically useless with respect to either vitamin deficiency. (Insofar as an elevated level of homocysteine was theretofore associated with illness, it was associated primarily with heart disease.[4] Pet. Br. at 3.) Similarly, knowing the correlation between an elevated level of total homocysteine and a cobalamin or folate deficiency cannot permit a diagnosis of either deficiency because the correlation is unconcerned with, and offers no instruction regarding, testing of body fluid. SA 30. Rather, the correlation is abstract knowledge, unrelated to either alteration and examination of body fluid or to diagnosis of individual patients.

In combination, however, the assay and correlation steps result in a useful diagnostic method. Here, it cannot be reasonably doubted that the "whole in some way exceeds

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unpatentability of one step or element of a claim renders the entire claim unpatentable. *Benson*, 409 U.S. at 67-68.

[4] Elevated levels of total homocysteine are also associated with renal disease, vitamin B6 deficiency, hypothyroidism, and lupus. *See, e.g.*, JA 250-51, 336-38, 355-56.

the sum of its parts." *Great Atl. & Pac. Tea Co.*, 340 U.S. at 152, *quoted in Diehr*, 450 U.S. at 193 n.15. As in *Diehr*, the application of what is assertedly a natural law (the correlation of elevated total homocysteine to cobalamin or folate deficiency) to a known process (the assay) has yielded a method for diagnosing such deficiencies that can save lives. Under *Diehr*, the subject matter of Claim 13 is therefore patentable.

Patentable subject matter includes "'anything under the sun that is made by man.'" *Diehr*, 450 U.S. at 182 (quoting legislative history of Patent Act of 1952); *see also Cuno Eng'g Corp. v. Automatic Devices Corp.*, 314 U.S. 84, 90 (1941) (subject matter must be not only "useful," but also an "invention"). Petitioner's single-minded focus on natural law – that is, on the inclusion in the correlation step of an asserted law of nature – obscures not only the assay step but also the inventiveness and utility of the steps' combination. *See* Pet. Br. Point I.A. Because of the risk inherent in such myopic attention to only one step in a process, *Diehr* warns that a court, in determining whether the subject matter of a process claim is patentable, must consider the claim "as a whole." *Diehr*, 450 U.S. at 188. Considered "as a whole," Claim 13 clearly satisfies the requirement that its subject matter be "made by man." The first step in the process – the assay – is undisputedly "made by man."[5] More important, the *result* of the process as a whole cannot exist in nature, because of the impossibility of diagnosing cobalamin or folate deficiency through unaided inspection of body fluid. Thus, the result – a medical diagnostic – is "made by man," and

[5] The validity of Respondents' patent claims concerning particular homocysteine assays is undisputed. Pet. Br. at 31-32.

hence patentable. Moreover, medical diagnosis based on any assay of a sample of body fluid from a patient – the overall accomplishment of Claim 13 – is clearly *not* a law of nature or natural phenomenon.

Insofar as a process, to be patentable, must "transform[]" an article into a "different state or thing," *Diehr*, 450 U.S. at 183, 184, Claim 13 clearly passes this test. The process described in Claim 13 requires assaying a body fluid for total homocysteine. An assay of a body fluid for total homocysteine necessitates substantial chemical and physical alteration of that fluid. For example, as demonstrated by the Detailed Description in the patent at issue, *see* SA 13-20 (col. 7, line 23, to col. 9, line 29; Examples II & III), a body fluid, such as a blood sample, must be obtained and mixed with an internal reference, such as an isotopically labeled molecule that reacts in a manner similar to homocysteine. This mixture is reacted with one or more reagents that break chemical bonds in the sample to free bound homocysteine groups. Protein is then removed through one or more steps, such as heat denaturation, ion exchange chromatography, or protein precipitation. Salts are subsequently removed from the sample with cation and anion exchange columns. Thereafter, the amino acids are concentrated and derivatized by reaction with additional chemicals that attach multiple silyl-containing groups to them. The resultant mixture is evaporated almost to dryness and injected onto a gas chromatograph/mass spectrophotometer for measurement. SA 13-20. This measurement is then used to calculate the total homocysteine level for the body fluid sample. In view of these many alterations of the blood sample, Claim 13 taken "as a whole," *Diehr*, 450 U.S. at 188, clearly satisfies

the transformation requirement. Petitioner's argument to the contrary is simply mistaken. *See* Pet. Br. at 27.

The inclusion in Claim 13 of a step requiring such tangible manipulation of a physical object – *i.e.*, the assay – puts Claim 13 squarely in the realm of patentable subject matter. This was the precise holding of *Diehr*: "[W]hen a claim containing a mathematical formula implements or applies that formula in a structure or process which, when considered as a whole, *is performing a function which the patent laws were designed to protect (e.g., transforming or reducing an article to a different state or thing)*, then the claim satisfies the requirements of § 101." 450 U.S. at 192 (emphasis added). More may be required of the claim ultimately to make it patentable; for example, the combination of the tangible manipulation with the natural law must be novel and non-obvious, and must satisfy the description, enablement, and definiteness requirements. *See* 35 U.S.C. §§ 102, 103, 112. But to clear the threshold of § 101, nothing more is required. *See Flook*, 437 U.S. at 593 ("The obligation to determine what type of discovery is sought to be patented must precede the determination of whether that discovery is, in fact, new or obvious."). As the *Diehr* Court held: "In this case, it may later be determined that the respondents' process . . . fails to satisfy the statutory conditions of novelty under § 102 and nonobviousness under § 103. A rejection on either of these grounds does not affect the determination that respondents' claims recited subject matter which was eligible for patent protection under § 101." 450 U.S. at 191.

Finally, even assuming that the correlation step represents a natural law, Claim 13 does not seek to pre-empt all use of the natural law, and does not cover every "substantial practical application" of the natural law. *See*

Benson, 409 U.S. at 71-72 (claimed process that involves mathematical formula is unpatentable if process includes every "substantial practical application" of mathematical formula, such that "the patent would wholly pre-empt the mathematical formula and in practical effect be a patent on the algorithm itself."). Specifically, Petitioner asserts that step one of Claim 13 concerns *any* assay, and thus that there are no substantial practical applications of the natural law that are not included within Claim 13. Pet. Br. at 29. Petitioner is mistaken, however. The assay claimed in step one is only of body fluids, not of other tissues. *See* SA 30 (describing step one as "assaying a body *fluid* for an elevated level of total homocysteine" (emphasis added)). Respondents' patent specification references "assays capable of determining levels of homocysteine in *body tissues,* preferably *body fluids*. . . ." SA 12 (emphasis added).[6] This portion of the specification thus demonstrates that assays of non-fluid tissues exist, and, given Claim 13's reference to assaying a body "fluid," SA 30, that diagnoses based on non-fluid assays are "substantial practical application[s]" involving no infringement whatever.[7]

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[6] The specification makes numerous additional references to body "tissue" and body "tissues." *See* SA 1, 10, 11, 12. Claim 5 explicitly references assay of "body tissue," as opposed to "body fluid." SA 30. Because Respondents clearly knew the difference between assay of tissue and assay of fluid, and because Claim 13 recites only assay of fluid, one must conclude that Claim 13 unequivocally excludes non-fluid assays. Respondents' intentionally disparate use of language supports the contention that Claim 13 does not include this "substantial practical application" and thus does not preempt the asserted natural law contained in the correlation step.

[7] Although the *Flook* Court held that the respondent's claim there was not patentable under § 101, the Court's holding was not based on

(Continued on following page)

B. A Reversal Would Call Into Question Innumerable Patents for Diagnostic Methods

Virtually every patent claim concerning a diagnostic method is based, explicitly or implicitly, on a correlation between a test result and a disease or medical condition. Thus, the repercussions for biotechnology, particularly diagnostics, if the decision below were reversed would be staggering. Hundreds, if not thousands, of patents would at once be called into question. Furthermore, since the research and development necessary to "personalize" medicines would be obstructed, many drugs that would aid in human health could be left unused. In a similar context, the *Diehr* Court rejected the argument that a claimed process is not patentable when it combines a previously known process with a natural law – that is, when the only newly invented step is a natural law: "To accept th[is] analysis . . . would, if carried to its extreme, make all inventions unpatentable because all inventions can be reduced to underlying principles of nature which, once known, make their implementation obvious." 450 U.S. at 189 n.12.

Patents have routinely been granted for diagnostic methods that, like Claim 13, consist of a non-specific "assay" or other measurement, followed by a "correlation"

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preemption. Indeed, the Court agreed with the respondent's argument that there were uses of the respondent's formula outside the respondent's own industry and thus that the claim did not violate the preemption prohibition. 437 U.S. at 589-90. Because Claim 13 is self-limited to body-fluid assays and does not include non-fluid assays, Petitioner's assertions that Claim 13 has a "prohibited preemptive sweep," Pet. Br. at 28, and that "Claim 13 covers every total homocysteine test no matter how it is performed," Pet. Br. at 29, are simply incorrect.

or functionally similar activity. Some of the more well-known examples include:

- **Prostate Specific Antigen ("PSA") test for prostate cancer:** Claim 10 of U.S. Patent No. 5,840,501, assigned on its face to Bayer Corp., identifies a method consisting of any "immunoassays" followed by a "correlat[ion]": "A method for monitoring the course of disease in a male patient diagnosed with prostate cancer, comprising the performance of a series of *immunoassays* over time to determine changes in the level of complexed prostate specific antigen (cPSA) in blood samples obtained from such patient, whereby changes in the cPSA blood level *correlate* with changes in disease status." (Emphasis added.) PSA is widely used to determine if a man has prostate cancer.

- **Test for HIV/AIDS:** Claim 1 of U.S. Patent No. RE38352, assigned on its face to Stanford University, identifies a method consisting of any test for a specific nucleic acid mutation, followed by a "correlat[ion]": "A method of evaluating the effectiveness of antiretroviral therapy of an HIV-infected patient comprising: collecting a plasma sample from an HIV-infected patient; and *determining* whether the plasma sample comprises nucleic acid encoding HIV reverse transcriptase having a mutation at codon 215, in which the presence of the mutation *correlates* positively with an accelerated immunologic decline of said patient compared to patients who do not have the mutation." (Emphasis added.) Mutations in the HIV virus within an infected individual are widely used (including by LabCorp) to help people find and take drugs that will make them better, and to avoid drugs that will make them sicker.

- **HER-2/neu test for breast and ovarian cancer:** Claim 1 of U.S. Patent No. 4,968,603, assigned on its face to the University of California, identifies a method consisting of any test for the amplification level of the HER-2/neu gene, followed by "classifying" an increased amplification relative to a "reference level": "A method for screening patients to determine disease status, said method comprising: *measuring* the level of amplification or expression of the HER-2/neu gene in a sample from a patient suffering from breast or ovarian adenocarcinoma; and *classifying* those patients having an increased level of amplification or expression of the HER-2/neu gene relative to a reference level characteristic of normal cells as being more likely to suffer disease relapse or having a decreased chance of survival." (Emphasis added.) HER-2/neu-related tests are widely used to determine which drug should be taken by a woman with breast cancer.

- **Test for neoplastic (i.e., cancerous) tissue:** Claim 7 of U.S. Patent No. 5,955,263, assigned on its face to Johns Hopkins University and Genzyme Corp., identifies a method consisting of comparing normal and abnormal proteins, and detecting a mutation-based alteration in the amino acid sequence wherein the alteration "indicates" neoplasia: "A method to aid in determining neoplasia of a tissue of a human, comprising: *comparing* (a) p53 proteins in a human tissue suspected of being neoplastic to (b) wild-type p53 proteins in a normal tissue of said human; detecting an alteration in the amino acid sequence between the p53 proteins, wherein the alteration is due to a mutation in a p53 gene in the human tissue suspected of being neoplastic, wherein the mutation is selected from the group consisting of:

> a point, deletion, missense, and frameshift mutation, *wherein an alteration in the amino acid sequence indicates neoplasia*." (Emphasis added.) Science Magazine named p53 the "molecule of the year." Mutations in p53 help doctors determine whether a tissue is cancerous.

That these examples are so familiar attests to the importance of incentivizing inventors through patent protection. This is the basis of the patent system – to provide incentive for new discoveries and their disclosure. Indeed, the critically important inventions listed above would not exist but for the patentability of assay-plus-correlation methods like that identified in Claim 13. And these constitute not only a small sampling of the vast array of diagnostic-method patents jeopardized by Petitioner's argument, but also a modest reflection of all the future inventions that might never come into being if the Court holds the subject matter of Claim 13 to be unpatentable.

II. ANY RULING IN THIS CASE SHOULD BE NARROW AND SHOULD NOT UPSET SETTLED LAW ON PATENTABLE SUBJECT MATTER

As detailed above, *amici* Perlegen and MDV believe that Claim 13 recites patentable subject matter. If the Court holds otherwise, however, its ruling should be narrow. In its prior discussion of the scope of patentable subject matter, the Court, acknowledging the author of the nation's first patent statute, has emphasized that "[t]he subject-matter provisions of the patent law have been cast in broad terms to fulfill the constitutional and statutory goal of promoting 'the Progress of Science and the useful Arts' with all that means for the social and economic

benefits envisioned by Jefferson." *Diamond v. Chakrabarty*, 447 U.S. 303, 315 (1980).

The existing limits on patentability, which include exceptions for "laws of nature, natural phenomena, and abstract ideas," *Diehr*, 450 U.S. at 185, already serve to promote the goal of invention and to avoid unnecessary judicial entanglement.[8] Any ruling in this case should not upset this settled law. In particular, any ruling should not upset settled law that diagnostic-method claims – including those involving an assay and correlation, which are common and of vital importance – are valid and patentable.

The scope of patentability should not be altered through this case for several reasons. First, as *amicus* United States explains, the record in this case is not sufficiently developed to permit comprehensive consideration of § 101's patentability requirements. U.S. Br. Point B. In fact, Petitioner did not argue below that the relevant patent was invalid under § 101, and Respondents had neither reason nor opportunity to introduce evidence to attempt to defeat a challenge under § 101. *Id.* Points B, C.2.b. Likewise, questions regarding Claim 13's patentability (if there were any) might be easily addressed simply by narrowing the court of appeals' interpretation of "correlation" in the second step of the claim. *Id.* Point C.3.

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[8] Of course, numerous additional statutory criteria further guard against the improper grant of a patent for matters undeserving of such protection: the novelty requirement of 35 U.S.C. § 102, the non-obviousness requirement of 35 U.S.C. § 103, and the enablement, written description, and definiteness requirements of 35 U.S.C. § 112.

Second, even if Claim 13 did not recite patentable subject matter as currently drafted, a minor modification could render it so. For example, one could add the simple step – beyond the abstract mental correlation between homocysteine levels in assayed body fluid and a deficiency of cobalamin or folate – of performing the correlation by computer. In other words, a third step would involve inputting a number (homocysteine levels), performing a correlation via an algorithm, and outputting another number (probability of a cobalamin and/or folate deficiency). With such a step added, Claim 13 would be analogous to other claims found to recite patentable subject matter. *See State St. Bank & Trust Co. v. Signature Fin. Group, Inc.*, 149 F.3d 1368, 1373 (Fed. Cir. 1998) ("[T]he transformation of data . . . by a machine through a series of mathematical calculations into a final [number], constitutes a practical application of a mathematical algorithm, formula, or calculation, because it produces a 'useful, concrete and tangible result.'" (quoting *In re Alappat*, 33 F.3d 1526, 1544 (Fed. Cir. 1994)).

III. ANY RULING IN THIS CASE SHOULD NOT UPSET THE CAREFUL BALANCE STRUCK UNDER OUR PATENT SYSTEM

The Constitution gives Congress "broad power to legislate to 'promote the Progress of Science and useful Arts. . . .'" *Chakrabarty*, 447 U.S. at 307 (quoting U.S. Const. art. I, § 8, cl. 8). The nation's patent laws "promote this progress by offering inventors exclusive rights for a limited period as an incentive for their inventiveness and research efforts." *Id.* (citations omitted). "The authority of Congress is exercised in the hope that '[t]he productive effort thereby fostered will have a positive effect on society

through the introduction of new products and processes of manufacture into the economy, and the emanations by way of increased employment and better lives for our citizens.'" *Id.* (citation omitted). The Patent Act of 1793, authored by Thomas Jefferson and, in relevant part, continuing substantially unchanged to the present, "embodied Jefferson's philosophy that 'ingenuity should receive a liberal encouragement.'" *Id.* at 308 (quoting 5 Writings of Thomas Jefferson 75-76 (Washington ed. 1871)).

Our patent system is therefore based on a careful balancing of various interests: To provide incentives for individuals and companies to conduct research and develop inventions, the Patent Act grants a patentee a limited exclusivity (in this case, for 17 years from the patent's issuance) to practice its invention. At the same time, as a *quid pro quo* for this limited exclusivity, a patentee must disclose detailed information about the manner and process of making and using the invention. 35 U.S.C. § 112 ("The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."). This disclosure requirement, in turn, ensures that the public receives the benefit of the patentee's research and development and thus provides a basis and incentive for other inventors to develop additional inventions around the patented one. *See generally Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 63 (1998) ("[T]he patent system represents a carefully crafted bargain that encourages both the creation and the public disclosure of

new and useful advances in technology, in return for an exclusive monopoly for a limited period of time").[9]

Research for diagnostics and other aspects of human health is funded either in an academic setting or by industry. The health-care industry relies on the very economic incentives provided by our patent system, including in large part by the patentability of claims such as Claim 13. If such claims were subject to invalidation as unpatentable, health-care companies would lose incentive to conduct research into basic diagnostics, to develop

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[9] In *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470 (1974), Chief Justice Burger described the balance as follows:

> The stated objective of the Constitution in granting the power to Congress to legislate in the area of intellectual property is to "promote the Progress of Science and useful Arts." The patent laws promote this progress by offering a right of exclusion for a limited period as an incentive to inventors to risk the often enormous costs in terms of time, research, and development. . . . In return for the right of exclusion – this "reward for inventions" – the patent laws impose upon the inventor a requirement of disclosure. To insure adequate and full disclosure so that upon the expiration of the 17-year period "the knowledge of the invention enures to the people, who are thus enabled without restriction to practice it and profit by its use," the patent laws require that the patent application shall include a full and clear description of the invention and "of the manner and process of making and using it" so that any person skilled in the art may make and use the invention. 35 U.S.C. § 112. When a patent is granted and the information contained in it is circulated to the general public and those especially skilled in the trade, such additions to the general store of knowledge are of such importance to the public weal that the Federal Government is willing to pay the high price of 17 years of exclusive use for its disclosure, which disclosure, it is assumed, will stimulate ideas and the eventual development of further significant advances in the art.

Id. at 480-81 (internal citations and footnote omitted).

personalized medicine tools and diagnostic systems, to validate them, and to have them approved by the FDA – all steps that are tremendously costly and necessary for the public to derive any benefit from new diagnostics. Likewise, venture capital and other financial firms would no longer have incentives to fund or invest in health-care companies that pursue the research, development, and regulatory approval of drugs and diagnostic systems. If there is no expectation of a limited right to exclusivity, industry will respond: These areas will be neglected in favor of other areas for which patent protection is still available.[10]

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[10] Harm from declaring claims like Claim 13 unpatentable is not limited to the loss of incentives for research and development. Rather, the diagnostics segment of the biotechnology industry – which industry generated $46 billion in revenues and 187,500 jobs in 2004, and which had a market capitalization of $488 billion in November 2005 – could be seriously jeopardized. *See* G. Steven Burrill, *Burrill's Biotech Outlook for 2006* . . . and a Look Back at 2005, PR Newswire, Dec. 22, 2005, *available at* http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=109&STORY=/www/story/12-22-2005/0004238848&EDATE=; *Biotechnology Industry Facts*, Biotechnology Industry Organization (2006), *available at* http://www.bio.org/speeches/pubs/er/statistics.asp. As described *supra* in Point I.B, if Claim 13 were found unpatentable, numerous other two-step diagnostic patents could be rendered void. At a minimum, companies holding those patents – and their investors and financial backers – would face uncertainty as to the value of their patents and the corresponding value of their businesses. It is unquestionable that a biotechnology company's value drops precipitously upon expiration of its patents, demonstrating the economic value afforded by patent protection. For example, Merck recently announced that it expected sales of its top-revenue product, the cholesterol drug Zocor, to drop from $4.35 billion in 2005 to $2.45 billion in 2006, when its patent expires in June 2006. *See Merck Plans More Cost-Cutting*, N.Y. TIMES, Dec. 16, 2005 at C5. A ruling finding claims like Claim 13 unpatentable would hasten such reduction of value for numerous companies, with devastating effects for the biotechnology industry.

Our patent system has already reached the proper balance of rewards and limits, particularly with regard to two-step diagnostic claims like Claim 13. The "reward" of patent protection is granted for only a limited time. The '658 patent, for example, expires in 2007. After that time, the patented method is freely available to the public. In addition, the reward is conditioned on disclosure of what has been invented – spurring competitors to search for other, better ways of achieving the same result. Indeed, such incentivized innovation is easily demonstrated in this case. Others in the field may use the detailed information disclosed by the '658 patent to help them design other, better methods to make the diagnosis of a cobalamin or folate deficiency – perhaps by using non-homocysteine markers, or by assaying homocysteine in a sample that is not a body fluid, or by some other entirely different method. At the same time, without the incentive of patent protection, an inventor would keep its knowledge secret, providing no benefit to the public.[11]

The ruling urged by Petitioner and various *amici* would upset the careful balance under our patent system. Indeed, their assertions ignore crucial aspects of the balance that has been struck – including the limited nature of patent protection and the full disclosure condition.

Contrary to Petitioner's suggestion, *see, e.g.*, Pet. Br. Point III, patent claims such as Claim 13 do not threaten doctors and never have. Claims in which a natural phenomenon is one, but not every, element of the claim are

[11] In addition, there would be no limit on how long the inventor may or would keep the knowledge from the public.

common. No doctor, however, has been sued for infringement of such a claim. The defendant in the instant case is Laboratory Corporation of America Holdings, a large industrial concern that profits from its vigorous marketing, promotion, and sale of an assay method that infringes the '658 patent.

Petitioner also wrongly hypothesizes that claims such as Claim 13 will lead to a decrease in testing and treatment. Pet. Br. Point III. To the contrary, testing and treatment are improving at an accelerating pace, due in large part to the incentives provided by patents. Following the successful sequencing of the human genome, new products are entering the market at a rapid pace. The future will see a large increase in diagnostics for cancer, genetic diseases, Alzheimer's disease, rheumatoid arthritis, cardiovascular disease, diabetes, osteoporosis, and schizophrenia. Numerous markers for cancer are being identified and commercialized. New markers for prostate cancer, such as PCA3, have been identified, and a new test is being developed for the prediction of breast cancer recurrence.[12]

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[12] *Amicus* American Clinical Laboratory Association ("ACLA") argues that a decision holding Claim 13 patentable would have inhibited testing such as that based on the correlation of increased risk of coronary heart disease with elevated blood levels of low-density lipoprotein ("LDL"), or testing based on the correlation of the presence of prostate cancer with an elevated level in body fluids of PSA. ACLA Br. Point II. Again, as an initial matter, doctors are not now being – and have never been – sued for infringement of diagnostic patents. In any event, if the patents envisioned by *amicus* had existed, they would have long since passed into the public domain due to the time limitation on patent protection. In addition, if the hypothetical patents had existed, the doomsday scenarios posited would not have been the necessary outcomes. Instead, with respect to LDL, the outcome could well have

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Similarly unavailing is Petitioner's contention that, "[i]f claim 13 is upheld, anyone who claims to be the first to discover a correlation can patent it – and thereby demand a royalty from anyone who even thinks about it. . . ." Pet. Br. at 46. As an initial matter, Claim 13 does not encompass a mere correlation; it is a two-step claim, one step of which includes a correlating step. In addition, "anyone who claims to be the first to discover a correlation" cannot obtain a patent solely for the correlation. Even a process with further steps, such as Claim 13, is subject to scrutiny for additional criteria: novelty, non-obviousness, proper inventorship, written description, enablement, and disclosure of best mode, all of which must be satisfied before a patent issues. In any event, as this case demonstrates, no royalty is being sought from a "thinker," whether a physician or an academic. Rather, the royalty is being sought from a corporate entity that profits from its marketing, promoting, and sale of tests that infringe the relevant patent. Meanwhile, it is the existence of the patent – encouraging invention and the concomitant required disclosure to obtain a patent – that promotes the very "thinking" sought by Petitioner. Without patent

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been an acceleration in the pace to find new predictors and markers for heart disease. If there had been a patent on the LDL method, it is entirely possible that more sophisticated, improved methods (*e.g.*, methods taking into account both LDL and high-density lipoprotein) would have been available to the public far earlier. Moreover, with respect to PSA, there have been many patented methods to make improvements in the assay – undoubtedly prompted by the hope of finding better, more reliable diagnostic methods to which an inventor would have a limited proprietary right. These existing patents, in turn, are encouraging the development of the next generation of PSA assays, as well as the development of completely new methods of detecting prostate cancer.

protection for claims such as Claim 13, those in the industry who discovered such methods would keep them secret and no one else – whether doctor, academic, or competitor – would have the benefit of such information. As a result, others would likely not be in a position to improve the assay or to find a different way to diagnose cobalamin or folate deficiency so that a new patent might issue for the improvement or new diagnostic.[13]

Petitioner and several *amici* also argue that claims such as Claim 13 chill research. Again, just the opposite is the case: Claim 13 provides incentive to develop better homocysteine assay methods. Such methods – additional, improved versions of patented methods – are routinely patented. A different and improved homocysteine assay is precisely what Claim 13 does not cover and could be patented by anyone who invented it. In addition, Claim 13 provides incentive to research and develop further diagnostics for cobalamin or folate deficiency that do not depend on homocysteine. Meanwhile, any remaining concern regarding infringement liability for researchers can be addressed through already-existing or new exceptions to patent liability, including for experimental use, *see Deuterium Corp. v. United States*, 19 Cl. Ct. 624, 631 (1990); clinical research, *see Merck KGaA v. Integra Lifesciences I, Ltd.*, 125 S. Ct. 2372 (2005) (discussing 35 U.S.C. § 271(e)); or medical use, *see* 35 U.S.C. § 287(c). Particularly in the case of clinical research, the exception is extremely broad. The exclusivity of Claim 13 – which ends in less than a year – can also be mitigated through

[13] In addition, Petitioner's concerns can be addressed, in any particular case, through the proof required to show direct infringement and the scope of any injunction entered.

cross-licensing, a daily phenomenon in the biotechnology industry. For example, anyone who invents a better assay can patent it and create leverage to cross-license the '658 patent, thus gaining access to patent rights.[14]

Finally, the discussion above demonstrates the weighty policy issues underlying our carefully structured and long-standing patent system. As shown in Point I, *supra*, Claim 13 fits easily within § 101's existing requirements for patentability. While Petitioners ask the Court to change this framework and to impose a further limitation on patentability, any such revision should be left to the Legislative branch. This Court so stated in *Chakrabarty*:

> The choice we are urged to make is a matter of high policy for resolution within the legislative process after the kind of investigation, examination, and study that legislative bodies can provide and courts cannot. That process involves the balancing of competing values and interests, which in our democratic system is the business of elected representatives. Whatever their validity, the contentions now pressed on us should be addressed to

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[14] The policy arguments proffered by *amici* Affymetrix and Professor Barton are generally directed at patentability of composition claims (and specifically claims covering isolated genes). *See* Affymetrix/Barton Br. Point II.B. There are strict, court-sanctioned Patent and Trademark Office Utility Guidelines for patenting a gene: The gene must be isolated out of its natural setting, and there must also be considerable evidence that the patentee understood the nature of the gene product coded for by the gene and its significance in physiological and biochemical function. *See In re Fisher*, 421 F.3d 1365, 1372-76 (Fed. Cir. 2005). The issue in the present case, however, is the patentability of a diagnostic-method claim, Claim 13. Case law regarding the patentability of method claims that include a natural phenomenon (*e.g.*, *Diehr*) focuses on a step-by-step method.

> the political branches of the Government, the Congress and the Executive, not to the courts.

447 U.S. at 317; *cf. Diehr*, 450 U.S. at 182 ("courts 'should not read into the patent laws limitations and conditions which the legislature has not expressed'").[15] Any ruling in this case should not upset settled law and expectations concerning the scope of patentability, and any limitation on the scope of patentable subject matter in the particular context of diagnostic claims should be left to Congress.

CONCLUSION

The judgment of the court of appeals should be affirmed.

Respectfully submitted,

GIDEON A. SCHOR
Counsel of Record
MEREDITH E. KOTLER
VERN NORVIEL
ERIC H. WITT
WILSON SONSINI GOODRICH & ROSATI
PROFESSIONAL CORPORATION
12 East 49th Street, 30th Floor
New York, NY 10017
(212) 999-5800

Counsel for Amici Curiae

[15] Congress can and does amend the patent law when it finds that a change is in the public interest. For example, in 1996, Congress exempted certain medical activity from giving rise to infringement liability. 35 U.S.C. § 287(c) (added by Pub. L. No. 104-208, § 616, 110 Stat. 3009, 3009-67 (Sept. 30, 1996)).

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LABORATORY CORPORATION OF AMERICA HOLDINGS (dba LabCorp),

Petitioner,

v.

METABOLITE LABORATORIES, INC. and COMPETITIVE TECHNOLOGIES, INC.,

Respondents.

On Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

BRIEF OF THE PUBLIC PATENT FOUNDATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

DANIEL B. RAVICHER
Executive Director
PUBLIC PATENT FOUNDATION, INC.
1375 Broadway, Suite 600
New York, New York 10018
(212) 796-0570

PROFESSOR JUSTIN HUGHES
Counsel of Record
Benjamin N. Cardozo
School of Law
55 Fifth Avenue
New York, New York 10003
(212) 790-0200
Counsel for Amicus Curiae

December 23, 2005

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INTEREST OF THE *AMICUS CURIAE*[1]

The Public Patent Foundation ("PUBPAT") is a not-for-profit legal services organization founded in 2003 to represent the public interest in the patent system, and most particularly the public's interests against the harms caused by wrongly issued patents and unsound patent policy. PUBPAT provides the general public and specific persons or entities otherwise deprived of access to the patent system with representation, advocacy, and education. It is funded by grants from the Rockefeller Foundation, the Echoing Green Foundation, the Rudolph Steiner Foundation and the Open Society Institute as well as donations from private individuals.

PUBPAT believes that the patent system can be improved through use of the patent system's existing legal structures. For example, the USPTO has consistently granted PUBPAT's requests for agency reexamination of particular patents that PUBPAT believes were wrongly issued. PUBPAT has also advocated for sound patent policy before this Court, the United States Court of Appeals for the Federal Circuit, the United States Patent & Trademark Office, the European Parliament, and the United States House of Representatives Subcommittee on Courts, the Internet, and Intellectual Property.

PUBPAT has an interest in this matter because the decision of this Court will have a significant effect on the

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[1] Pursuant to Supreme Court Rule 37.6, *amicus* states that no counsel for a party authored this brief in whole or in part, and that no person or entity, other than *amicus curiae* and its counsel made a monetary contribution to the preparation or submission of this brief. Written consent of the parties was obtained and will be filed with the Clerk of the Court in accordance with Supreme Court Rule 37.3.

public interest represented by PUBPAT. More specifically, PUBPAT has an interest in ensuring that this Court's established limits on patentable subject matter are maintained.

SUMMARY OF ARGUMENT

Almost twenty-five years have passed since this Court last addressed the core issues of patentable subject matter. In that time, the Court of Appeals for the Federal Circuit has replaced this Court's substantive standard with a more formalistic approach that has expanded the definition of patentable subject matter to include virtually anything. This expansion by the Federal Circuit conflicts with this Court's precedent and, as such, merits remediation.

In addition, there are two other issues that should be considered when addressing patentable subject matter. First, allowing claims that effectively cover all uses of a law of nature or abstract idea frustrates the patent system's goal of disclosure. Second, patent claims that restrict communication regarding abstract ideas or laws of nature are contrary to the First Amendment.

I. THE COURT OF APPEALS FOR THE FEDERAL CIRCUIT HAS IMPERMISSIBLY VEERED FROM THIS COURT'S PRECEDENT REGARDING PATENTABLE SUBJECT MATTER.

Almost twenty-five years have passed since this Court last addressed the core issues of patentable subject matter. *Cf. J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124 (2001) (addressing whether utility patents

may be issued for plants). In that time, the Court of Appeals for the Federal Circuit has replaced this Court's substantive standard with a more formalistic approach that has expanded the definition of patentable subject matter to include virtually anything. This expansion by the Federal Circuit is judicially erroneous and merits remediation.

A. This Court's Precedent Sets Out Limits on Patentable Subject Matter.

Confronted with the rise of new technologies, this Court has addressed the issue of patentable subject matter several times. *Gottschalk v. Benson*, 409 U.S. 63 (1972); *Parker v. Flook*, 437 U.S. 584 (1978); *Diamond v. Chakrabarty*, 447 U.S. 303 (1980); *Diamond v. Diehr*, 450 U.S. 175 (1981). Since before the Civil War, this Court has consistently made it clear that subject matter which would have the practical effect of preempting a law of nature, mathematical formula, or abstract idea is ineligible for patent protection. *O'Reilly v. Morse*, 56 U.S. (15 How.) 62, 113 (1854); *Benson*, 409 U.S. at 71. This age-old and time-tested precedent effectively establishes a penumbra of ineligibility for patent protection to safeguard the fundamental policy that laws of nature and abstract ideas be left unrestrained by patents.

To be eligible for patent protection, "[a] process itself, not merely the mathematical algorithm, must be new and useful." *Flook*, 437 U.S. at 591; *Funk Bros. Seed Co. v. Kalo Co.*, 333 U.S. 127, 130 (1948) ("He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes. If there is to be invention from such a discovery, it must come from the

application of the law of nature to a new and useful end."). This Court stated in *Flook* that it is "incorrect [to] assume[] that if a process application implements a principle in some specific fashion, it automatically falls within the patentable subject matter of § 101." *Id.* at 593. This Court explained that such an assumption is based on an impermissibly narrow interpretation of its precedent, including specifically *Benson,* and is "untenable" because "[i]t would make the determination of patentable subject matter depend simply on the draftsman's art and would ill serve the principles underlying the prohibition against patents for 'ideas' or phenomena of nature." *Id.*

In alignment with *Benson* and *Flook*, this Court's decision in *Diehr* held that structures or processes must, when considered as a whole, perform functions intended to be covered by patent law in order to be eligible for patent protection. 450 U.S. at 192. Although *Diehr* may have effectively overruled *Flook's* "point of novelty" test, it nonetheless followed and upheld the core holdings of both *Benson* and *Flook*. *Id.* at 190, 191-193 (*citing Benson* and *Flook* repeatedly and *stating* "[o]ur reasoning in *Flook* is in no way inconsistent with our reasoning here").

Benson, *Flook*, *Diehr* and the other decisions of this Court regarding patentable subject matter consistently established that the inquiry into whether subject matter is eligible for patenting is one of substance and function, not form. This Court requires that one look, not simply at the language of the patent claim to see if it recites a structure of multiple steps or components, but also at the practical effect of the claim to see if it in fact covers – or otherwise would restrict the public's use of – a principle, law of nature, abstract idea, mathematical formula, mental process or other abstract intellectual concept.

This substantive standard ensures that skilled patent draftsmanship is not capable of overcoming one of the most core principles of patent law recognized by this Court for more than 150 years that "[a] principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented, as no one can claim in either of them an exclusive right." *Le Roy v. Tatham*, 55 U.S. (14 How.) 156, 175 (1853); *Funk Bros.*, 333 U.S. at 130; *Benson*, 409 U.S. at 67 ("[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work").

B. The Federal Circuit Has Strayed from This Court's Limits on Patentable Subject Matter.

Many scholars have noted that the creation of the Federal Circuit "did away as a practical matter with Supreme Court jurisdiction in patent cases." Kenneth W. Dam, *The Economic Underpinnings of Patent Law*, 23 J. Legal Stud. 247, 270 (1994). For example, through a series of decisions, the Federal Circuit has abandoned the substantive based standard established by this Court for determining patentable subject matter and replaced it with a more expansive formalistic approach that looks only to see whether a patent claim contains some structure or has some minimal practical utility. The Federal Circuit's form-over-substance approach has come to include virtually anything within patentable subject matter.

Initially, the Federal Circuit used the opinions of legal commentators to justify straying from *Benson* and *Flook*. *Arrhythmia Research Tech., Inc. v. Corazonix Corp.*, 958

F.2d 1053, 1057 n.4 (1992) ("Although commentators have differed in their interpretations of *Benson, Flook,* and *Diehr,* it appears to be *generally agreed* that these decisions represent *evolving views* of the Court, and that the reasoning in *Diehr* not only elaborated on, but in part superseded, that of *Benson* and *Flook*") (emphasis added) (*citing* R.L. Gable & J.B. Leaheey, *The Strength of Patent Protection for Computer Products,* 17 Rutgers Computer & Tech. L.J. 87 (1991); D. Chisum, *The Patentability of Algorithms*, 47 U. Pitt. L. Rev. 959 (1986)). Evidently, the Federal Circuit felt that "general agreement" amongst legal commentators justified abandoning this Court's precedent. In reaching this conclusion, the Federal Circuit also ignored the *Diehr* Court's statement that its decision there was in accord with *Benson* and *Flook*. *Diehr*, 450 U.S. at 185-193.

Also in *Arrhythmia*, the Federal Circuit stated that, "claims to a specific process or apparatus . . . will *generally satisfy* section 101." *Id.* at 1058 (emphasis added). This Court's precedent does not – in fact – support the proposition that any process or apparatus "generally satisfies" the requirements of patentable subject matter. *Diehr*, 450 U.S. at 193 ("[a] mathematical formula as such is not accorded the protection of our patent laws . . . and this principle cannot be circumvented by attempting to limit the use of the formula to a particular technological environment") (citing *Benson* and *Flook*). The new "general rule" promulgated in *Arrhythmia* was a major step in the Federal Circuit's departure from this Court's precedent regarding patentable subject matter.

Roughly two years later, the Federal Circuit said that this Court's precedent on patentable subject matter was too unclear to follow. *In re Alappat*, 33 F.3d 1526, 1543

n.19 and n.20 (Fed. Cir. 1994) ("The Supreme Court has not been clear", "The Supreme Court has not set forth, however, any consistent or clear explanation", "the understandable struggle that the [Supreme] Court was having in articulating a rule"). Contrary to the Federal Circuit's characterizations, however, this Court's precedent on patentable subject matter is plainly clear: the analysis is one of substance, not form, and asks whether a patent claim effectively preempts a law of nature, natural phenomenon or abstract idea.

After disregarding this Court's precedent as "unclear," the Federal Circuit substituted its own formalistic approach, which finds that virtually anything is eligible for patenting. *Id.* at 1542 ("[t]he use of the expansive term 'any' in § 101 represents Congress's intent not to place any restrictions on the subject matter for which a patent may be obtained"). The Federal Circuit's approach conflicts with this Court's precedent. For example, it ignores the firm statement in *Diehr* that "[a] mathematical formula does not suddenly become patentable subject matter simply by having the applicant acquiesce to limiting the reach of the patent for the formula to a particular technological use." 450 U.S. at 193.

In support of its holding, the Federal Circuit cited this Court's *Chakrabarty* decision for the proposition that, "Congress intended § 101 to extend to 'anything under the sun that is made by man.'" *Id.* (citing *Chakrabarty*, 447 U.S. 303, 309). However, the Federal Circuit then went much farther than *Chakrabarty's* holding by saying, "Thus, it is improper to read into § 101 limitations as to the subject matter that may be patented where the legislative history does not indicate that Congress clearly intended such limitations." *Id.* But such was precisely *not*

this Court's holding in *Chakrabarty*. Immediately following the language in *Chakrabarty* quoted by the Federal Circuit, this Court continued to say that, "[t]his is *not* to suggest that § 101 has *no* limits or that it embraces every discovery." 447 U.S. at 309 (emphasis added). In support of that statement, this Court referred to *Flook*, *Benson*, *Funk Bros.* and other cases, and not to any legislative history. Thus, this Court's precedent clearly shows that there are indeed limits on patentable subject matter beyond those expressly stated by Congress. The Federal Circuit's ruling to the contrary was error.

Indeed, *Alappat* was a highly divided *en banc* decision, wherein several members of the Federal Circuit recognized the judicial error being made. *Id.* at 1552, 1562 (Archer, C.J., *dissenting* "Losing sight of the forest for the structure of the trees, the majority today holds that any claim reciting a precise arrangement of structure satisfies 35 U.S.C. § 101. . . . [T]he rationale that leads to this conclusion and the majority's holding that Alappat's rasterizer represents the invention of a machine are illogical, inconsistent with precedent and with sound principles of patent law, and will have untold consequences", "the majority's test under § 101 that looks simply to whether specific structure is claimed is [] inconsistent with Supreme Court precedent").

Since *Alappat*, the Federal Circuit has continued its expansion of patentable subject matter through the implementation of its formalistic approach. *State St. Bank & Trust Co. v. Signature Fin. Group*, 149 F.3d 1368 (Fed. Cir. 1998) (holding that anything with a "practical utility" is patentable subject matter); *AT&T Corp. v. Excel Communications, Inc.*, 172 F.3d 1352 (Fed. Cir. 1999). The effect of this expansion has been to eliminate the *Benson-Flook-Diehr*

limitation on patentable subject matter, because any semi-competent patent drafter can easily craft claims that have some structure or a "practical utility" that nonetheless preempt the use of a law of nature, abstract idea or natural phenomenon. The Federal Circuit believes such claims are patentable subject matter. This Court's precedent mandates that they are not.

In this case, the practical effect of claim 13 is to preclude the use of a law of nature, namely the natural correlation in mammalian physiology between elevated levels of total homocysteine and certain vitamin B deficiencies.[2] This is because, although the claim contains another element, an "assaying" step, that element is so general and broad that it has no practical limiting effect. Anyone performing the "correlating" step must, in some way, assay body fluid for an elevated total homocysteine level. Thus, under this Court's precedent, claim 13 is not patentable subject matter. In contrast, under the Federal Circuit's formalistic approach that anything with some structure or a "practical utility" is patent eligible, claim 13 would be patentable subject matter, as detecting vitamin B deficiencies is surely a "practical utility."

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[2] Indeed, the application originally was more direct in its claim to the law of mammalian physiology concerning the homocysteine-cobalamin/folate relationship. During the application process the applicant expressly told the examiner that "[a]s applicants are the first to detect cobalamin or folate deficiency by assaying body fluids for total homocysteine, it is believed that they are entitled to a claim of equivalent scope, not limited to any particular steps or methods." Pet. App. 9a.

II. IN ORDER TO PROMOTE THE PATENT SYSTEM'S GOAL OF DISCLOSURE, A CLAIM THAT EFFECTIVELY COVERS ALL USES OF A LAW OF NATURE OR ABSTRACT IDEA SHOULD BE INELIGIBLE FOR PATENT PROTECTION.

Both patent and copyright laws are constitutionally bound "[t]o Promote Progress in Science and the Useful Arts." Patent law does this by providing (i) an incentive for the *achievement* of technological advances, (ii) an incentive for the commercialization of those advances, and (iii) an incentive for the *disclosure* of advances that are achieved. In the absence of the patent system, many inventions would be protected by trade secrecy, interfering with norms of science that favor prompt disclosure of new information, particularly new discoveries in basic science. As this Court said in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327 (1945):

> The primary purpose of our patent system is not reward of the individual but the advancement of the arts and sciences. Its inducement is directed to disclosure of advances in knowledge which will be beneficial to society; it is not a certificate of merit, but an incentive to disclosure.

Id. at 330-331 (citations removed). Similarly, in *Markman v. Westview Instruments, Inc.*, this Court emphasized that disclosure must occur not simply because "the limits of the patent must be known" to third parties, but also for "the encouragement of the inventive genius of others." 517 U.S. 370, 390 (1996). *See also Universal Oil Products Co. v. Globe Oil & Refining Co.*, 322 U.S. 471, 484 (1944); Rebecca Eisenberg, *Patents and the Progress of Science*, 56 U. CHI L. REV. 1017, 1028 (1989) (concluding that the patent

system "facilitates disclosure by creating rights in inventions that survive disclosure"); Justin Hughes, *The Philosophy of Intellectual Property*, 77 Geo. L. J. 287, 316 (1988) (patent rights coupled with disclosure leads to expansion of the "commons" of ideas).

But such disclosure will do little or nothing to promote further progress – there will be no "encouragement of the inventive genius of others" – unless subsequent researchers are allowed to use the basic scientific teachings and discoveries disclosed in the patent. That those basic scientific teachings and discoveries remain unprotected is not just happenstance. There can be no "inventing around" a patent unless the patent discloses the basic scientific principles upon which the invention relies – those principles being broader than the invention claimed in the patent. This is the principal way by which "patent disclosure advances the 'Progress of . . . useful Arts' by permitting societal resources to be put to their best use in advancing more quickly beyond the patentee's contribution." Katherine Strandburg, *What Does the Public Get?: Experimental Use and the Patent Bargain*, 2004 Wisc. L. Rev. 81, 112 (2004).

To promote continuing progress in science and the useful arts, both patent and copyright delineate what may be protected ***and*** what may ***not*** be protected. In copyright, ideas and facts are unprotectable subject matter – things that may not be "propertized." *Feist Publications, Inc. v. Rural Telephone Service*, 499 U.S. 340 (1991) (facts are not copyrightable); *Harper & Row, Publishers, Inc. v. Nation Enterprises*, 471 U.S. 539, 547 (1985) ("no author may copyright facts or ideas"); *Baker v. Selden*, 101 U.S. 99 (1879) (methods cannot be copyrighted).

As discussed in Part I, this Court's patent precedent has made it clear that scientific truths, laws of nature, natural phenomena, and abstract ideas are unprotectable subject matter. *Rubber Tip Pencil Company v. Howard*, 87 U.S. 498, 507 (1874) ("an idea of itself is not patentable"); *Mackay Radio & Tel. Co. v. Radio Corp. of America*, 306 U.S. 86, 94 (1939) ("a scientific truth, or the mathematical expression of it, is not patentable invention"); *Benson*, 409 U.S. at 67; *Flook*, 437 U.S. at 589; *Diehr*, 450 U.S. at 185 (stating that laws of nature, natural phenomena, and abstract ideas are excluded from patent protection). In both copyright and patent law, these realms of unprotectable subject matter have been established by courts, not Congress[3] – a point that, as discussed in Part I, the Federal Circuit overlooked in *In re Alappat*.

In copyright law, the merger doctrine is an important mechanism for drawing the line between what can and cannot be propertized. "[G]iven the dilemma either of protecting original expression . . . when that protection can be leveraged to grant an effective monopoly over the idea thus expressed, or of making the idea free to all with the concomitant result that the plaintiff loses effective copyright protection . . . copyright chooses the latter course." Melville B. Nimmer & David Nimmer, NIMMER ON COPYRIGHT § 13.03[B][3] at 13-79 (2005); *Veeck v. Southern*

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[3] While the bar of copyright on "ideas" was codified in 1976 at 17 U.S.C. § 102(b), that section is silent on copyright not extending to "facts." Yet this Court in *Feist* was crystal clear that "facts are not copyrightable" remains a "well-established proposition," 499 U.S. at 344, just as this Court has consistently held that "[e]xcluded from such patent protection are laws of nature, natural phenomena, and abstract ideas," *Diamond v. Diehr*, 450 U.S. at 185, despite silence on this point in the Patent Act.

Bldg. Code Cong. Int'l Inc., 293 F.3d 791 (5th Cir. 2002) (*en banc*), *cert. denied,* 539 U.S. 969 (2003) (where privately created model building code became binding municipal code, expression and the "fact" of municipal law "merged" and code may be freely copied); *Kern River Gas Transmission Co. v. Coastal Corp.*, 899 F.2d 1458 (5th Cir.), *cert. denied*, 498 U.S. 952 (1990) (expression of map showing location of pipeline and actual location of pipeline "merged" so that map was unprotected); *Morrissey v. Proctor & Gamble Co.*, 379 F.2d 675, 678 (1st Cir. 1967) (idea of particular kinds of sweepstakes and expression of sweepstakes rules merged where copyrighting expression "could exhaust all possibilities of future use of the substance").

This Court first enunciated the basic notion of the merger doctrine in *Baker v. Selden*, *supra,* concerning the scope of exclusive rights granted to the author of a copyrighted book "exhibit[ing] and explain[ing] a peculiar system of book-keeping." 101 U.S. at 100. This Court concluded that the exclusive rights of copyright extended only to expression itself and not to the teachings of the accounting method. In his opinion for this Court, Justice Bradley noted that protectable expression – the diagrams – would be, to some degree, dedicated to the public if those diagrams were necessary for practice of the uncopyrighted ideas:

> [a]nd where the art [the book] teaches cannot be used without employing the methods and diagrams used to illustrate the book, or such as are similar to them, such methods and diagrams are to be considered as necessary incidents to the art, and given therewith to the public.

Id. at 103. If the diagrams – a form of expression – and the unprotected accounting method "merge," then no copyright over the diagrams will prevent an individual from using the accounting method, even if that means they reproduce the diagrams in their own calculations.

In *Herbert Rosenthal Jewelry Corp. v. Kalpakian*, 448 F.2d 738 (9th Cir. 1971), the Ninth Circuit found that the defendant could not be liable for infringement of the plaintiff's copyright in a jewelry pin in the shape of a bee because the bee-shaped pin was quite life-like and, therefore, any other life-like bee pins would be "substantially similar" in expression to the plaintiff's jewelry. The court denied relief to the plaintiff succinctly stating the merger doctrine:

> When the "idea" and its "expression" are thus inseparable, copying the "expression" will not be barred, since protecting the "expression" in such circumstances would confer a monopoly of the "idea" upon the copyright owner free of the conditions and limitations imposed by the patent law.

Id. at 742. Of course, one of those fundamental "limitations imposed by the patent law" is that the exclusive rights of patent law do not extend to laws of nature – the issue in this case being that claim 13 would seal off a law of nature in that observing any instantiation of the general law of nature would violate the patent.

This Court has consistently recognized "the historic kinship between patent law and copyright law." *Sony v. Universal City Studios*, 464 U.S. 417, 439 (1984). *See also Fox Film Corp. v. Doyal*, 286 U.S. 123, 131 (1932) (concerning Court's determinations of tax treatment of royalties, "what we have said as to the purposes of the

Government in relation to copyrights applies as well, *mutatis mutandis*, to patents which are granted under the same constitutional authority to promote the progress of science and useful arts"). In both *Sony* and last Term's *Grokster* decision, this Court looked to patent law for development of rules of third party liability in copyright law. *MGM Studios Inc. v. Grokster, Ltd.*, 125 S. Ct. 2764, 2779 (2005) (drawing further parallel between third party liability in patent and copyright law).

While patent law draws a different line between what can be protected and what cannot be protected, it is nonetheless appropriate to look to copyright's merger doctrine as a model of how to resolve situations where a patent claim is arguably within patentable subject matter but would nonetheless *unquestionably* "exhaust all possibilities of future use of the substance" of the disclosure – in this case, a basic law of mammalian physiology. *Morrissey*, 379 F.2d at 678. To paraphrase *Herbert Rosenthal*, when the claimed patentable "process" and the underlying "law of nature" are inseparable, use of the "process" should not be barred, since protecting the "process" in such circumstances would confer a monopoly on the "law of nature" – violating a basic tenet of patent law. *See also* Eileen M. Kane, *Splitting the Gene: DNA Patents and the Genetic Code*, 71 Tenn. L. Rev. 707, 753-754 (2004) (proposing that patent claims which preempt laws of nature be limited, when necessary, "with the use of the merger doctrine from copyright law").

In this particular case, upholding claim 13 would, in effect, prevent the patent from generating or communicating *any* information that could help other would-be inventors because *every* inference about homocysteine – cobalamin/folate correlation would infringe the claim. If

claim 13 is upheld – and has the scope set out by the Federal Circuit – the principal disclosure in the patent – use of a basic law of mammalian physiology – will be preempted. Indeed, this is just the sort of problem presaged by *Benson*, where this Court said that otherwise patentable subject matter is not eligible for a patent if the "practical effect" of the patent would cover a law of nature. 409 U.S. at 71-72. *Benson*'s "practical effect" test to bar patenting of what would otherwise appear to be patentable subject matter is, in effect, an inchoate patent law version of copyright law's merger doctrine.

Further, LabCorp's inducement liability was based on distributing informational materials that "state[d] that elevated total homocysteine correlates to cobalamin/folate deficiency." Pet. App. 15a and again at 16a. In other words, LabCorp's liability was based on *disclosing* the law of nature that is *disclosed* in the patent. LabCorp's publications stated a law of nature: "that elevated homocysteine correlates to cobalamin/folate deficiency," Pet. App. 15a, which is no different than information freely available from the National Institutes of Health ("NIH"). The NIH website describes the basic teaching of claim 13 in its own descriptions of the relationship of homocysteine and folate or cobalamin deficiency as follows:

> "An elevated level of homocysteine in the blood, a risk factor for cardiovascular disease, also can result from folate deficiency."
>
> "A deficiency of folate, vitamin B_{12} or vitamin B_6 may increase blood levels of homocysteine, and folate supplementation has been shown to decrease homocysteine levels and to improve endothelial function."

National Institutes of Health, Office of Dietary Supplements, http://ods.od.nih.gov/factsheets/folate.asp, last visited December 23, 2005. One can find similar information in all types of medical literature, which unquestionably should not be held in any way to violate private patent rights.[4] Although inducement liability can properly attach to the distribution of physical materials in addition to information, punishing the dissemination of information alone through inducement liability would negate patent law's own goal of disclosure. In fact, to do so would result in the USPTO itself being an indirect infringer of all the patents it issues.

III. PATENT CLAIM CONSTRUCTIONS THAT RESTRICT COMMUNICATION REGARDING ABSTRACT IDEAS OR LAWS OF NATURE ARE CONTRARY TO THE FIRST AMENDMENT.

This Court has long held that communication enjoys First Amendment protection unless it falls within certain narrow categories of expression that are of "such slight social value that any benefit that may be derived from them is clearly outweighed by the social interest in order and morality." *Chaplinsky v. New Hampshire*, 315 U.S. 568, 572 (1942). It is difficult to dispute that communication of scientific ideas and facts has significant social value. *Compare Miller v. California*, 413 U.S. 15, 24 (1973) (noting that the definition of obscenity will not apply to

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[4] *See, e.g.* Folic Acid Deficiency, eMedicine, http://www.emedicine.com/med/topic802.htm, last visited December 23, 2005 ("the significance of folic acid deficiency is compounded further by the following attributes: • An association of folate deficiency with elevated homocysteine, leading to increased arteriosclerosis risks").

expressive material if it has serious "scientific value"). Accordingly, lower courts have identified as black letter law the principle that "the First Amendment protects scientific expression and debate just as it protects political and artistic expression." *Universal City Studios, Inc. v. Corley*, 273 F.2d 429, 446-47 (2nd Cir. 2001).

In this case, the Federal Circuit found direct infringement of claim 13 based "*solely* on whether the physicians perform the correlating step." Pet. App. 13a (emphasis added). The Federal Circuit's decision could thus be taken to construe as an infringer any person who discussed the relationship between elevated homocysteine and deficiencies in B vitamins. At a minimum, it would appear that a person who discussed the correlation after looking at an elevated homocysteine level in a particular assay (which they performed or was performed on their behalf) would infringe. This finding of infringement for a purely speech based activity seems contrary to First Amendment principles.

In the copyright context, this Court has mediated tension with the First Amendment through the idea/expression dichotomy, which "strike[s] a definitional balance between the First Amendment and the Copyright Act by permitting free communication of facts while still protecting the author's expression." *Eldred v. Ashcroft*, 537 U.S. 186, 220 (2003) (citing *Harper & Row*, 471 U.S. at 556). The *Eldred* Court further noted that "[d]ue to this distinction, every idea, theory, and fact in a copyrighted work becomes instantly available for public exploitation at the moment of publication." *Id.*

As discussed in Part II, patent law has no explicit counterpart to copyright law's idea/expression dichotomy

and its associated doctrine of merger. However, this Court's longstanding exclusion of laws of nature and abstract ideas from patentable subject matter has played a somewhat parallel function. Were laws of nature and abstract ideas to be patentable subject matter, scientific expression could be seriously restricted in violation of the First Amendment. Thus, when addressing the issue of patentable subject matter, which is but one area of increasing tension between patent law and the First Amendment, it is important to be mindful of the consequence such decisions will have on the Freedom of Speech.

CONCLUSION

For the foregoing reasons, this Court should uphold its limitations on patentable subject matter and remand this case for further examination of the patent in light of the bar on patenting laws of nature, scientific truths, and abstract ideas.

Respectfully submitted,

DANIEL B. RAVICHER
Executive Director
PUBLIC PATENT FOUNDATION, INC.
1375 Broadway, Suite 600
New York, New York 10018
(212) 796-0570

PROFESSOR JUSTIN HUGHES
Counsel of Record
Benjamin N. Cardozo
School of Law
55 Fifth Avenue
New York, New York 10003

Counsel for Amicus Curiae

December 23, 2005

Per Curiam

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SUPREME COURT OF THE UNITED STATES

No. 04–607

LABORATORY CORPORATION OF AMERICA HOLDINGS, DBA LABCORP, PETITIONER *v.* METABOLITE LABORATORIES, INC., ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

[June 22, 2006]

PER CURIAM.

The writ of certiorari is dismissed as improvidently granted.

THE CHIEF JUSTICE took no part in the consideration or decision of this case.

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[June 22, 2006]

JUSTICE BREYER, with whom JUSTICE STEVENS and JUSTICE SOUTER join, dissenting.

This case involves a patent that claims a process for helping to diagnose deficiencies of two vitamins, folate and cobalamin. The process consists of using any test (whether patented or unpatented) to measure the level in a body fluid of an amino acid called homocysteine and then noticing whether its level is elevated above the norm; if so, a vitamin deficiency is likely.

The lower courts held that the patent claim is valid. They also found the petitioner, Laboratory Corporation of America Holdings (LabCorp), liable for inducing infringement of the claim when it encouraged doctors to order diagnostic tests for measuring homocysteine. The courts assessed damages. And they enjoined LabCorp from using any tests that would lead the doctors it serves to find a vitamin deficiency by taking account of elevated homocysteine levels.

We granted certiorari in this case to determine whether the patent claim is invalid on the ground that it improperly seeks to "claim a monopoly over a basic scientific relationship," Pet. for Cert. i, namely, the relationship between homocysteine and vitamin deficiency. The Court has dismissed the writ as improvidently granted. In my

view, we should not dismiss the writ. The question presented is not unusually difficult. We have the authority to decide it. We said that we would do so. The parties and *amici* have fully briefed the question. And those who engage in medical research, who practice medicine, and who as patients depend upon proper health care, might well benefit from this Court's authoritative answer.

I

A

The relevant principle of law "[e]xclude[s] from . . . patent protection . . . laws of nature, natural phenomena, and abstract ideas." *Diamond* v. *Diehr*, 450 U. S. 175, 185 (1981). This principle finds its roots in both English and American law. See, *e.g.*, *Neilson* v. *Harford*, Webster's Patent Cases 295, 371 (1841); *Le Roy* v. *Tatham*, 14 How. 156, 175 (1853); *O'Reilly* v. *Morse*, 15 How. 62 (1854); *The Telephone Cases*, 126 U. S. 1 (1888). The principle means that Einstein could not have "patent[ed] his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity." *Diamond* v. *Chakrabarty*, 447 U. S. 303, 309 (1980). Neither can one patent "a novel and useful mathematical formula," *Parker* v. *Flook*, 437 U. S. 584, 585 (1978), the motive power of electromagnetism or steam, *Morse*, *supra*, at 116, "the heat of the sun, electricity, or the qualities of metals," *Funk Brothers Seed Co.* v. *Kalo Inoculant Co.*, 333 U. S. 127, 130 (1948).

The justification for the principle does not lie in any claim that "laws of nature" are obvious, or that their discovery is easy, or that they are not useful. To the contrary, research into such matters may be costly and time-consuming; monetary incentives may matter; and the fruits of those incentives and that research may prove of great benefit to the human race. Rather, the reason for the exclusion is that sometimes *too much* patent protection can impede rather than "promote the Progress of

Science and useful Arts," the constitutional objective of patent and copyright protection. U. S. Const., Art. I, §8, cl. 8.

The problem arises from the fact that patents do not only encourage research by providing monetary incentives for invention. Sometimes their presence can discourage research by impeding the free exchange of information, for example by forcing researchers to avoid the use of potentially patented ideas, by leading them to conduct costly and time-consuming searches of existing or pending patents, by requiring complex licensing arrangements, and by raising the costs of using the patented information, sometimes prohibitively so.

Patent law seeks to avoid the dangers of overprotection just as surely as it seeks to avoid the diminished incentive to invent that underprotection can threaten. One way in which patent law seeks to sail between these opposing and risky shoals is through rules that bring certain types of invention and discovery within the scope of patentability while excluding others. And scholars have noted that "patent law['s] exclu[sion of] fundamental scientific (including mathematical) and technological principles," (like copyright's exclusion of "ideas") is a rule of the latter variety. W. Landes & R. Posner, The Economic Structure of Intellectual Property Law 305 (2003). That rule reflects "both . . . the enormous potential for rent seeking that would be created if property rights could be obtained in [those basic principles] and . . . the enormous transaction costs that would be imposed on would-be users." *Id.*, at 305–306; cf. *Nichols* v. *Universal Pictures Corp.*, 45 F. 2d 119, 122 (CA2 1930) (L. Hand, J.).

Thus, the Court has recognized that "[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts are . . . the basic tools of scientific and technological work." *Gottschalk* v. *Benson*, 409 U. S. 63, 67 (1972). It has treated fundamental scien-

tific principles as "part of the storehouse of knowledge" and manifestations of laws of nature as "free to all men and reserved exclusively to none." *Funk Bros.*, *supra*, at 130. And its doing so reflects a basic judgment that protection in such cases, despite its potentially positive incentive effects, would too often severely interfere with, or discourage, development and the further spread of useful knowledge itself.

B

In the 1980s three university doctors, after conducting research into vitamin deficiencies, found a correlation between high levels of homocysteine in the blood and deficiencies of two essential vitamins, folate (folic acid) and cobalamin (vitamin B_{12}). They also developed more accurate methods for testing body fluids for homocysteine, using gas chromatography and mass spectrometry. They published their findings in 1985. They obtained a patent. And that patent eventually found its commercial way into the hands of Competitive Technologies, Inc. (CTI), and its licensee Metabolite Laboratories, Inc. (Metabolite), the respondents here.

The patent contains several claims that cover the researchers' new methods for testing homocysteine levels using gas chromatography and mass spectrometry. Supp. App. 30. In 1991, LabCorp (in fact, a corporate predecessor) took a license from Metabolite permitting it to use the tests described in the patent in return for 27.5% of related revenues. Their agreement permitted LabCorp to terminate the arrangement if "a more cost effective commercial alternative is available *that does not infringe a valid and enforceable claim* of" the patent. App. 305 (emphasis added).

Until 1998, LabCorp used the patented tests and paid royalties. By that time, however, growing recognition that elevated homocysteine levels might predict risk of heart

disease led to increased testing demand. Other companies began to produce alternative testing procedures. And LabCorp decided to use one of these other procedures—a test devised by Abbott Laboratories that LabCorp concluded was "far superior." *Id.*, at 167 (testimony of Peter Wentz).

LabCorp continued to pay royalties to respondents whenever it used the patented tests. But it concluded that Abbott's test did not fall within the patent's protective scope. And LabCorp consequently refused to pay royalties when it used the Abbott test. *Id.*, at 237 (payment eliminated due to "change in methodology").

In response, respondents brought this suit against LabCorp for patent infringement and breach of the license agreement. They did not claim that LabCorp's use of the Abbott test infringed the patent's claims describing methods for testing for homocysteine. Instead, respondents relied on a broader claim not limited to those tests, namely claim 13, the sole claim at issue here. That claim—set forth below in its entirety—seeks patent protection for:

> "A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> "assaying a body fluid for an elevated level of total homocysteine; and
>
> "correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate." Supp. App. 30.

Claim 13, respondents argued, created a protected monopoly over the process of "correlating" test results and potential vitamin deficiencies. The parties agreed that the words "assaying a body fluid" refer to the use of any test at all, whether patented or not patented, that determines whether a body fluid has an "elevated level of total homocysteine." And at trial, the inventors testified that claim

13's "correlating" step consists simply of a physician's recognizing that a test that shows an elevated homocysteine level—by that very fact—shows the patient likely has a cobalamin or folate deficiency. App. 108–111 (testimony of Dr. Sally Stabler); *id.*, at 131–148 (testimony of Robert Allen). They added that, because the natural relationship between homocysteine and vitamin deficiency was now well known, such "correlating" would occur automatically in the mind of any competent physician. *Id.*, at 137–138 (same).

On this understanding of the claim, respondents argued, LabCorp was liable for inducing doctors to infringe. More specifically, LabCorp would conduct homocysteine tests and report the results measured in micromoles (millionths of a mole) per liter (symbolized μmol/L). Doctors, because of their training, would know that a normal homocysteine range in blood is between 7 and 22 μmol/L (and in urine between 1 and 20 μmol/L), Supp. App. 14, and would know that an elevated homocysteine level is correlated with a vitamin deficiency. Hence, in reviewing the test results, doctors would look at the μmol/L measure and automatically reach a conclusion about whether or not a person was suffering from a vitamin deficiency. Claim 13 therefore covered *every* homocysteine test that a doctor reviewed. And since LabCorp had advertised its tests and educated doctors about the correlation, LabCorp should be liable for actively inducing the doctors' infringing acts. See 35 U. S. C. §271(b).

The jury found LabCorp liable on this theory. The District Court calculated damages based on unpaid royalties for some 350,000 homocysteine tests performed by LabCorp using the Abbott method. The court also enjoined LabCorp from performing "any homocysteine-only test, including, without limitation homocysteine-only tests via the Abbott method." App. to Pet. for Cert. 36a–37a (internal quotation marks omitted).

LabCorp appealed. It argued to the Federal Circuit that the trial court was wrong to construe claim 13 so broadly that infringement took place "every time a physician does nothing more than look at a patient's homocysteine level." Corrected Brief for Appellant in No. 03–1120 (CA Fed.), p. 28 (hereinafter Brief for Appellant). Indeed, if so construed (rather than construed, say, to cover only *patented* tests), then claim 13 was "invalid for indefiniteness, lack of written description, non-enablement, anticipation, and obviousness." *Id.*, at 38. LabCorp told the Federal Circuit:

> "If the Court were to uphold this vague claim, anyone could obtain a patent on any scientific correlation—that there is a link between fact A and fact B—merely by drafting a patent claiming no more than 'test for fact A and correlate with fact B' . . . . Claim 13 does no more than that. If it is upheld, CTI would improperly gain a monopoly over a basic scientific fact rather than any novel invention of its own. The law is settled that no such claim should be allowed. *See, e.g.*, *Diamond* v. *Diehr*, 450 U. S. 175 (1981); . . . Chisum on Patents §1.03[6]." *Id.*, at 41.

The Federal Circuit rejected LabCorp's arguments. It agreed with the District Court that claim 13's "correlating" step simply means "relating total homocysteine levels to cobalamin or folate deficiency, a deficiency in both, or a deficiency in neither." 370 F. 3d 1354, 1363 (2004). That meaning, it said, is "discernable and clear"; it is definite, it is described in writing, and it would enable virtually anyone to follow the instruction it gives. And that is sufficient. *Id.*, at 1366–1367. The Court did not address LabCorp's argument that, *if so construed*, claim 13 must be struck down as an improper effort to obtain patent protection for a law of nature.

Moreover, the Circuit concluded, because any competent

doctor reviewing test results would automatically correlate those results with the presence or absence of a vitamin deficiency, virtually every doctor who ordered and read the tests was a direct infringer. And because LabCorp "publishes . . . Continuing Medical Education articles" and other pieces, which urge doctors to conduct the relevant tests and to reach a conclusion about whether a patient is suffering from a vitamin deficiency based upon the test results, LabCorp induces infringement. *Id.*, at 1365. Finally, the court rejected LabCorp's challenge to the injunction. *Id.*, at 1372.

LabCorp filed a petition for certiorari. Question Three of the petition asks "[w]hether a method patent . . . directing a party simply to 'correlate' test results can validly claim a monopoly over a basic scientific relationship . . . such that any doctor necessarily infringes the patent merely by thinking about the relationship after looking at a test result." Pet. for Cert. i. After calling for and receiving the views of the Solicitor General, 543 U. S. 1185 (2005), we granted the petition, limited to Question Three.

II

The question before us is whether claim 13, as construed and applied in the way I have described in Part I–B, is invalid in light of the "law of nature" principle, described in Part I–A. I believe that we should answer that question. There is a technical procedural reason for not doing so, namely, that LabCorp did not refer in the lower courts to §101 of the Patent Act, which sets forth subject matter that is patentable, and within the bounds of which the "law of nature" principle most comfortably fits. See 35 U. S. C. §101 (patent may be obtained for "any new and useful process, machine, manufacture, or composition of matter"); *Flook*, 437 U. S., at 588–589. There is also a practical reason for not doing so, namely, that we might benefit from the views of the Federal Circuit, which did

not directly consider the question. See, *e.g.*, *United States* v. *Bestfoods*, 524 U. S. 51, 72–73 (1998).

Nonetheless, stronger considerations argue for our reaching a decision. For one thing, the technical procedural objection is tenuous. LabCorp argued the essence of its present claim below. It told the Federal Circuit that claim 13 as construed by the District Court was too "vague" because that construction would allow "anyone" to "obtain a patent on any scientific correlation;" it would permit the respondents "improperly [to] gain a monopoly over a basic scientific fact" despite "settled" law "that no such claim should be allowed." Brief for Appellant 41 (citing *Diehr*, 450 U. S., at 1185; 1 D. Chisum, Patents §1.03[6]) (2006 ed.) (hereinafter Chisum). LabCorp explicitly stated in its petition for certiorari that, "if the Court allows the Federal Circuit opinion to stand . . . [respondents] would improperly gain monopolies over basic scientific facts rather than any novel inventions of their own." Pet. for Cert. 25 (citing *Diehr*, *supra*; *Gottschalk*, 409 U. S. 63; *Funk Bros.*, 333 U. S. 127; *Mackay Radio & Telegraph Co.* v. *Radio Corp. of America*, 306 U. S. 86 (1939)). And after considering the Solicitor General's advice not to hear the case (primarily based upon LabCorp's failure to refer to 35 U. S. C. §101), we rejected that advice, thereby "necessarily consider[ing] and reject[ing] that contention as a basis for denying review." *United States* v. *Williams*, 504 U. S. 36, 40 (1992).

For another thing, I can find no good practical reason for refusing to decide the case. The relevant issue has been fully briefed and argued by the parties, the Government, and 20 *amici*. The record is comprehensive, allowing us to learn the precise nature of the patent claim, to consider the commercial and medical context (which the parties and *amici* have described in detail), and to become familiar with the arguments made in all courts. Neither the factual record nor the briefing suffers from any

significant gap. No party has identified any prejudice due to our answering the question. And there is no indication that LabCorp's failure to cite §101 reflected unfair gamesmanship.

Of course, further consideration by the Federal Circuit might help us reach a better decision. Lower court consideration almost always helps. But the thoroughness of the briefing leads me to conclude that the extra time, cost, and uncertainty that further proceedings would engender are not worth the potential benefit.

Finally, I believe that important considerations of the public interest—including that of clarifying the law in this area sooner rather than later—argue strongly for our deciding the question presented now. See Part IV, *infra*.

III

I turn to the merits. The researchers who obtained the present patent found that an elevated level of homocysteine in a warm-blooded animal is correlated with folate and cobalamin deficiencies. As construed by the Federal Circuit, claim 13 provides those researchers with control over doctors' efforts to use that correlation to diagnose vitamin deficiencies in a patient. Does the law permit such protection or does claim 13, in the circumstances, amount to an invalid effort to patent a "phenomenon of nature"?

I concede that the category of non-patentable "phenomena of nature," like the categories of "mental processes," and "abstract intellectual concepts," is not easy to define. See *Flook, supra*, at 589 ("The line between a patentable 'process' and an unpatentable 'principle' is not always clear"); cf. *Nichols*, 45 F. 2d, at 122 ("[W]e are as aware as anyone that the line [between copyrighted material and non-copyrightable ideas], wherever it is drawn, will seem arbitrary"). After all, many a patentable invention rests upon its inventor's knowledge of natural phenomena;

many "process" patents seek to make abstract intellectual concepts workably concrete; and all conscious human action involves a mental process. See generally 1 Chisum §1.03, at 78–295. Nor can one easily use such abstract categories directly to distinguish instances of likely beneficial, from likely harmful, forms of protection. Cf. FTC, To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy, ch. 3, p. 1 (Oct. 2003) (hereinafter FTC) (collecting evidence that "issues of fixed cost recovery, alternative appropriability mechanisms, and relationships between initial and follow-on innovation" vary by industry); Burk & Lemley, Policy Levers in Patent Law, 89 Va. L. Rev. 1575, 1577–1589 (2003) ("Recent evidence has demonstrated that this complex relationship [between patents and innovation] is . . . industry-specific at each stage of the patent process").

But this case is not at the boundary. It does not require us to consider the precise scope of the "natural phenomenon" doctrine or any other difficult issue. In my view, claim 13 is invalid no matter how narrowly one reasonably interprets that doctrine.

There can be little doubt that the correlation between homocysteine and vitamin deficiency set forth in claim 13 is a "natural phenomenon." That is what the petitioners argue. It is what the Solicitor General has told us. Brief for United States as *Amicus Curiae* 19 (filed Dec. 23, 2005) ("The natural relationship between elevated homocysteine and deficiencies in the B vitamins is an unpatentable 'principle in natural philosophy or physical science'") (quoting *Morse*, 15 How., at 116)). Indeed, it is close to what the respondents concede. Brief for Respondents 31 ("The correlation between total homocysteine and deficiencies in cobalamin and folate that the Inventors discovered could be considered, standing alone, a 'natural phenomenon' in the literal sense: It is an observable aspect of biochemistry in at least some human populations").

The respondents argue, however, that the correlation is nonetheless patentable because claim 13 packages it in the form of a "process" for detecting vitamin deficiency, with discrete testing and correlating steps. They point to this Court's statements that a "process is not unpatentable simply because it contains a law of nature," *Flook*, 437 U. S., at 590; see also *Gottschalk*, 409 U. S., at 67, and that "an *application* of a law of nature . . . to a known . . . process may well be deserving of patent protection." *Diehr*, 450 U. S., at 187. They add that claim 13 is a patentable "application of a law of nature" because, considered as a whole, it (1) "entails a physical transformation of matter," namely, the alteration of a blood sample during whatever test is used, Brief for Respondents 33 (citing *Cochrane* v. *Deener*, 94 U. S. 780, 788 (1877); *Gottschalk, supra*, at 70), and because it (2) "produces a 'useful, concrete, and tangible result,'" namely, detection of a vitamin deficiency, Brief for Respondents 36 (citing *State Street Bank & Trust Co.* v. *Signature Financial Group, Inc.*, 149 F. 3d 1368, 1373 (CA Fed 1998)).

In my view, however, the cases to which respondents refer do not support their claim. Neither *Cochrane* nor *Gottschalk* can help them because the process described in claim 13 is *not* a process for transforming blood or any other matter. Claim 13's process instructs the user to (1) obtain test results and (2) think about them. Why should it matter if the test results themselves were obtained through an unpatented procedure that involved the transformation of blood? Claim 13 is indifferent to that fact, for it tells the user to use any test at all. Indeed, to use virtually any natural phenomenon for virtually any useful purpose could well involve the use of empirical information obtained through an unpatented means that might have involved transforming matter. Neither *Cochrane* nor *Gottschalk* suggests that that fact renders the phenomenon patentable. See *Cochrane, supra*, at 785 (upholding

process for improving quality of flour by removing impurities with blasts of air); *Gottschalk, supra*, at 71–73 (rejecting process for converting numerals to binary form through mathematical formula).

Neither does the Federal Circuit's decision in *State Street Bank* help respondents. That case does say that a process is patentable if it produces a "useful, concrete, and tangible result." 149 F. 3d, at 1373. But this Court has never made such a statement and, if taken literally, the statement would cover instances where this Court has held the contrary. The Court, for example, has invalidated a claim to the use of electromagnetic current for transmitting messages over long distances even though it produces a result that seems "useful, concrete, and tangible." *Morse, supra*, at 16. Similarly the Court has invalidated a patent setting forth a system for triggering alarm limits in connection with catalytic conversion despite a similar utility, concreteness, and tangibility. *Flook, supra*. And the Court has invalidated a patent setting forth a process that transforms, for computer-programming purposes, decimal figures into binary figures—even though the result would seem useful, concrete, and at least arguably (within the computer's wiring system) tangible. *Gottschalk, supra*.

Even were I to assume (purely for argument's sake) that claim 13 meets certain general definitions of process patentability, however, it still fails the one at issue here: the requirement that it not amount to a simple natural correlation, *i.e.*, a "natural phenomenon." See *Flook, supra*, at 588, n. 9 (even assuming patent for improved catalytic converter system meets broad statutory definition of patentable "process," it is invalid under natural phenomenon doctrine); *Diehr*, 450 U. S., at 184–185 (explaining that, even if patent meets all other requirements, it must meet the natural phenomena requirement as well).

At most, respondents have simply described the natural

law at issue in the abstract patent language of a "process." But they cannot avoid the fact that the process is no more than an instruction to read some numbers in light of medical knowledge. Cf. *id.*, at 192 (warning against "allow[ing] a competent draftsman to evade the recognized limitations on the type of subject matter eligible for patent protection"). One might, of course, reduce the "process" to a series of steps, *e.g.*, Step 1: gather data; Step 2: read a number; Step 3: compare the number with the norm; Step 4: act accordingly. But one can reduce *any* process to a series of steps. The question is what those steps embody. And here, aside from the unpatented test, they embody only the correlation between homocysteine and vitamin deficiency that the researchers uncovered. In my view, that correlation is an unpatentable "natural phenomenon," and I can find nothing in claim 13 that adds anything more of significance.

IV

If I am correct in my conclusion in Part III that the patent is invalid, then special public interest considerations reinforce my view that we should decide this case. To fail to do so threatens to leave the medical profession subject to the restrictions imposed by this individual patent and others of its kind. Those restrictions may inhibit doctors from using their best medical judgment; they may force doctors to spend unnecessary time and energy to enter into license agreements; they may divert resources from the medical task of health care to the legal task of searching patent files for similar simple correlations; they may raise the cost of healthcare while inhibiting its effective delivery. See Brief for American Clinical Laboratory Association as *Amicus Curiae* 8–13.

Even if Part III is wrong, however, it still would be valuable to decide this case. Our doing so would help diminish legal uncertainty in the area, affecting a "substantial

number of patent claims." See Brief for United States as *Amicus Curiae* 12–14 (filed Aug. 26, 2005). It would permit those in the medical profession better to understand the nature of their legal obligations. It would help Congress determine whether legislation is needed. Cf. 35 U. S. C. §287(c) (limiting liability of medical practitioners for performance of certain medical and surgical procedures).

In either event, a decision from this generalist Court could contribute to the important ongoing debate, among both specialists and generalists, as to whether the patent system, as currently administered and enforced, adequately reflects the "careful balance" that "the federal patent laws . . . embod[y]." *Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489 U. S. 141, 146 (1989). See also *eBay Inc.* v. *MercExchange, L. L. C.*, 547 U. S. ___, ___ (2006) (slip op., at 2) (KENNEDY, J., concurring); FTC, ch. 4, at 1–44; Pollack, The Multiple Unconstitutionality of Business Method Patents: Common Sense, Congressional Consideration, and Constitutional History, 28 Rutgers Computer & Technology L. J. 61 (2002); Pitofsky, Antitrust and Intellectual Property: Unresolved Issues at the Heart of the New Economy, 16 Berkeley Technology L. J. 535, 542–546 (2001).

For these reasons, I respectfully dissent.